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The Practical Management of Dizziness

JOHN R. LINDSAY, M.D., Chicago

• The problem of dizziness is greatly simplified if: (1) A definite routine is followed in the history taking and the steps of the examination; (2) the examination is done in two stages; and (3) a simple classification is used in cases of dizziness of vestibular origin whereby three groups are distinguished on the basis of localization of the origin. The etiologic diagnosis is thereby narrowed down to a relatively few possibilities.

The treatment consists of measures to relieve the symptoms and to reverse the underlying disease which produced the symptoms.

DIZZINESS is one of the common complaints to be heard in a physician's office. It may occur in a variety of systemic diseases as well as in the more localized disturbances of the inner ear.

The management of the patient with dizziness often presents a somewhat confusing and time-consuming problem. The problem arises mainly because of the broad field to be covered in differential diagnosis and the frequent lack of definite clues to indicate the cause.

The first objective in dealing with this complaint is to determine, if possible, whether the dizziness is true vertigo arising from the vestibular system in the ear and its central nervous connections, or whether it arises from some other system of the body which is concerned with equilibrium.

Ocular disturbances, especially if they are of recent origin, may affect equilibrium, particularly during motion, and cause a complaint of confusion or lightheadedness. They do not cause a sense of rotation or turning such as occurs in vertigo of vestibular origin.

The body depends also on kinesthetic sense for maintenance of position and equilibrium. A disturbance of this sense in such diseases as locomotor ataxia or syringomyelia may cause impairment of equilibrium during motion.

Diseases of the circulatory system are more frequently a source of a complaint that may be confused with true dizziness or vertigo. Persons who are subject to attacks of syncope may use the term "dizzy spell" or "blacking out." Certain syndromes such as the carotid sinus syndrome and Stokes-Adams syndrome may cause the complaint of "dizziness." These circulatory disturbances are not likely to cause a true sense of rotation or movement. If there has been a definite loss of consciousness lasting at least for a few moments, the attack is probably not due to a vestibular disturbance but the origin is likely to be found in the circulatory system or more rarely in the cerebral cortex.

Dizziness is a subjective sensation and may be met with in persons with an unstable psychic make-up. There is real doubt as to whether vestibular vertigo with its accompanying nystagmus, ataxia and vegetative symptoms can be caused entirely by psychic disturbance. There has been ample evidence that Meniere's disease or hydrops of the labyrinth

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tends to be aggravated by psychic stress, but, in the absence of such a disease entity, it is doubtful if true vestibular vertigo can occur purely on a psychogenic basis. Psychogenic dizziness will not be described as a clear-cut sense of movement such as occurs in labyrinthine vertigo, nor will the patient give a description of a postural vertigo such as is frequent in organic vestibular disturbances.

DIAGNOSIS

The history obtained from the patient is the most important step in the diagnosis of dizziness. It must include specific questioning to bring out all the characteristics of the dizzy spell and to indicate whether vertigo occurs only when certain positions are assumed or certain changes in position made. The history must also include questioning regarding possible related signs and symptoms.

Much of the confusion connected with the management of vertigo can be avoided by the use of a definite routine of examination and by using a simple classification as a basis for diagnosis.

A routine method of examination that serves well in cases of dizziness is as follows:

1. Routine ear, nose and throat examination. Function of cranial nerves. Tests for incoordination, Rombergism, past pointing, etc.
2. Hearing tests.
3. Spontaneous nystagmus.
4. Positional nystagmus.
5. Caloric tests of labyrinthine function.
6. Routine laboratory work including urinalysis and blood counts. Blood pressure.

It has been found advisable to divide the examination into two sessions, leaving the hearing tests and caloric tests usually for the second session, by which time the laboratory work has been completed.

CLASSIFICATION

In order to be of practical value any classification of dizziness must be relatively simple. It has been found advantageous to consider vertigo of vestibular origin in three main groups on the basis of localization. If the case can be classed as belonging to one of these three groups the etiologic diagnosis then becomes somewhat simplified. The various causes can be considered under these three groups.

GROUP 1

This group includes cases in which the vertigo is known to arise from the central nervous system. The localization to the central nervous system is seldom made on the basis of the ear findings alone but is usually based on the associated central nervous system symptoms and signs. Dizziness of central origin is due mainly to involvement of the vestibular nuclei or the directly associated nervous pathways.

In some instances the vertigo may be rapid in onset resembling the vertigo which arises from disease of the peripheral labyrinth. This is true particularly of vascular lesions. In many instances however the vertigo associated with central nervous system disease is postural in character and is brought on when the body and head assume certain positions. The practical importance of postural vertigo is that such information can be readily elicited in the history and the complaint can usually be substantiated by putting the patient through the positions which he has found to cause the symptoms. The reproduction of the vertigo and the observation of a positional nystagmus at that time indicates the existence of an organic lesion of the vestibular system. Some of the central nervous system diseases which commonly produce vertigo are:

1. Inflammatory disease such as encephalitis, meningoencephalitis or brain abscess.
2. Vascular lesions, particularly those affecting the posterior inferior cerebellar artery or related vessels.
3. Tumors, particularly when located in the posterior fossa or affecting posterior fossa structures by pressure or distortion.
4. Degenerative disease, of which the most frequent is multiple sclerosis.

The etiologic diagnosis in the case of the central nervous system lesion is usually dependent upon associated symptoms and signs of central nervous system disease.

In many instances examination of the function of the ear, both as to hearing and vestibular function, will contribute information essential to the localization and determining the cause.

The dizziness which comes with central nervous system disease may require symptomatic treatment if onset is acute and rapid. Complete rest, and the use of drugs such as Dramamine® (meclizine hydrochloride) Bonamine® (dimenhydrinate) and chlorpromazine are of value. In the case of postural vertigo the patient soon learns to avoid the positions that bring on the symptom.

Of practical importance is the fact that a progressive disease such as tumor or multiple sclerosis may cause dizziness, and particularly the postural type of dizziness, as the initial symptom.

GROUP 2

A second group of cases can be localized in origin to the peripheral vestibular mechanism or the 8th nerve. This localization is based principally on the association of auditory disturbances with the onset of the dizziness. While it is true that dizziness

may come from the peripheral vestibular mechanism without tinnitus or deafness, there is usually no way in which this can be established. There are many causes for vertigo arising from the inner ear and 8th nerve. Some of these causes are problems for specialists but a few are of direct interest to general physicians as well.

Labyrinthitis due to spread of infection from the middle ear has been a common cause of severe dizziness in the past but need not enter into the present discussion.

Tumors involving the ear or the 8th nerve, although not common, need to be considered because the early diagnosis of such tumors, particularly acoustic neurinoma and cerebellopontile angle tumors, is essential if cure is to be obtained.

Dizziness may not be a prominent symptom, whereas impaired hearing and tinnitus in one ear usually are the first complaints. A good rule to follow is that every person with unilateral nerve deafness of fairly recent development should have a complete examination both of hearing and of the vestibular function, always with the possibility of tumor in mind.

There are some systemic diseases which occasionally are complicated by a disturbance of the labyrinth. Blood diseases in particular such as severe anemia or leukemia occasionally affect the inner ear. Allergic reactions sometimes produce inner ear disturbance. Certain drugs will also cause impaired hearing and dizziness in susceptible persons. Quinine and its derivatives and salicylates are two of the classic examples.

Of especial interest to medical practitioners are two types of inner ear or vestibular disturbance. One is the sudden or apoplectic attack of dizziness, deafness and tinnitus in a previously healthy ear. There may be one attack in a lifetime. Another is the syndrome of repeated attacks of dizziness associated with fluctuating degrees of deafness and tinnitus which is now known as Meniere's disease.

The sudden attack of dizziness, deafness and tinnitus in the previously healthy ear may occur in any age period from the second decade on. The cause in some cases is infection, in some it is cardiovascular disease and in some it is not known.

Some virus diseases apparently have the capacity to set up a reaction within the inner ear. The best known examples are measles and mumps and some other acute infectious diseases.

The measles virus[2, 3] has been found to set up labyrinthitis in the endolymphatic labyrinth, which injures the sense organs directly. While histopathologic proof has been obtained only in the case of measles, the clinical evidence indicates that some infections of the upper respiratory tract, probably viral in nature, may also affect the labyrinth.

It also seems that the inner ear or 8th nerve may be the site of a toxic reaction to a focus of infection elsewhere—in the paranasal sinuses, for example.

Vascular disturbances in the inner ear are probably the most frequent cause of an isolated sudden attack of dizziness and deafness. Little information is available about the pathologic change in the human ear in such cases, but there is clinical evidence that a vascular accident, probably occlusion, may produce a severe dizzy spell accompanied by varying degrees of permanent damage to both auditory and vestibular function.

Vascular occlusion probably produces a fairly typical clinical picture in that the onset is rapid, recovery is slow, requiring sometimes many months before dizziness is fully cleared up, and there is a varying degree of permanent damage.

A sudden attack of deafness and dizziness without any evident cause sometimes occurs in persons in their twenties and even earlier. Recovery from the dizziness is gradual, hearing may improve but some degree of permanent damage is the general rule.

TREATMENT

Symptomatic treatment includes absolute quiet, sedation and the use of Dramamine, Bonamine, chlorpromazine or related drugs with maintenance of fluid balance by intravenous infusion if necessary. Vasodilator drugs such as nicotinic acid and intravenous histamine or procaine have been tried but with questionable effect. If some function remains there is usually spontaneous improvement in hearing for the first two months.

The syndrome of recurrent attacks of dizziness, along with deafness and tinnitus is a more common condition. It is known as Meniere's disease in most medical writings at present because of the clear-cut clinical syndrome and the evidence that the pathological condition known as idiopathic hydrops of the labyrinth is present in the inner ear in such cases. Meniere's disease is greatly feared by the patient because of the incapacitating spells of dizziness, which are unpredictable as to frequency, duration or severity. The deafness and tinnitus follow a more consistent pattern. The more constant clinical findings are the hearing loss for low tones and the low pitched "roaring" tinnitus, both of which fluctuate in severity from time to time. In about 90 per cent of cases the disease is unilateral. The diagnosis can not be made on the basis of dizzy spells alone.

The cause of Meniere's disease is not yet known. It seems probable that some disturbance in the mechanism of endolymph production must occur and that some alteration in the constitution of the endolymph thereby takes place. The theory cur-

rently favored is that this disturbance in endolymph occurs as a result of autonomic imbalance affecting the blood vessels in the cochlea. There is some clinical evidence that mental or psychic stress as well as nervous fatigue tend to aggravate the condition.

The medical treatment of Meniere's disease has been relatively unsatisfactory. Various medicines have been used with the object of preventing the dizzy spells, including low salt diet, diuretics, vasodilator drugs such as histamine and nicotinic acid and blocking agents such as Banthine and many other drugs. Clinical investigations by Perlman and Goldinger[3, 4] seemed to refute the theory that the disease could be influenced by the salt intake and the use of diuretics.

Routine medical treatment used by the author includes advice to avoid the use of particularly salty foods but not to restrict the use of salt in ordinary quantities in cooking. Nicotinic acid is prescribed routinely, partly because it is simple for the patient to use at home. Fifty milligrams twice a day is the usual dose. So far no convincing evidence has been observed that any of the medical therapy used has had any consistent value. It is important to control the patient's activities, for example, to avoid overwork and to encourage regularity and moderation in habits of eating and resting. A mild barbiturate is usually helpful. It would appear from clinical observation that mental stress and fatigue are important factors to avoid. It is possible that the psychological effect of the general management of the patient may be the most important factor. At least 90 per cent of patients under medical management show definite improvement and may be able to continue normal activities.

During a dizzy spell different methods of treatment have been tried. Intravenous infusions of histamine and of procaine have been used with indefinite results. Procaine block of the cervical sympathetic ganglia have also been tried without definite effect. Dramamine by mouth, or intravenously if necessary, is of definite value. Bed rest and avoidance of movement is essential.

In the past 15 years the author has observed that between 5 and 10 per cent of patients with Meniere's disease have not been sufficiently controlled by ordinary medical therapy and have needed some other type of treatment.

Procaine block of the stellate ganglion has not proven successful in our hands.

Streptomycin in carefully controlled dosage carried to the point where the vestibular responses are abolished has been used in a few selected cases with good results in all. Streptomycin therapy unfortunately gives the patient an ataxia in order to give protection against dizzy spells. This ataxia is soon compensated for in younger patients but less readily in patients in the sixth decade and over. The author is of the opinion that streptomycin therapy is to be considered mainly in bilateral cases in which the dizzy spells are causing definite disability, provided the patient is under about 50 years of age.

Surgical operation to destroy the inner ear is the treatment of choice in unilateral cases in which there is continuing disability from dizzy spells. Complete destruction of the labyrinth is preferable to any attempt at partial destruction. It is also preferable to section the vestibular nerve, for the risk is less and tinnitus is more likely to be relieved.

GROUP 3

In addition to the cases of dizziness which can be localized either to the peripheral or to the central vestibular mechanism, there is a somewhat larger group in which definite localization may not be possible. These are the cases in which patients complain of vertigo but have no deafness or tinnitus and no evidence of any disease of the central nervous system. They may or may not have some associated systemic disease which might suggest an explanation for the dizziness. In this group the patient may have a single attack of dizziness which clears up and does not recur; he may occasionally have repeated attacks or he may have dizziness which is brought on only when he gets into certain positions.

In the event that the patient states that he gets dizzy only when he sits up in the morning, or when he turns on one side in bed, or when he stoops over or looks upward for some moments, it is usually possible to reproduce the dizziness by placing him in these particular positions. These postural tests will confirm the patient's complaint. If the dizziness can be reproduced and is accompanied by nystagmus, it is clear that there is organic vestibular disturbance.

There are a number of conditions that can cause dizzy spells or dizziness of the kind in this group.

Acute infection usually of the virus type frequently causes vertigo either in the form of an attack which may require several days for recovery or in the form of postural vertigo. Occasionally there appear to be mild epidemics of such infections. Disease of this kind has been named "vestibular neuronitis" by Hallpike and associates.

Cardiovascular disease may also cause this type of dizziness. The vertigo which is caused by a vascular accident or occlusion tends to follow a particular pattern. There is an acute onset of vertigo and it remains severe for a few days then gradually recedes. As the symptom decreases it tends to become a postural symptom only. It is characteristic

of this type that several months and even one or two years may be required for complete recovery from the dizziness. The site of the vascular lesion may not be evident. An attack of dizziness of this type in a patient who has definite cardiovascular disease is probably an indication of vascular occlusion. While spontaneous recovery from such an attack is the general rule, it is not uncommon to have other central nervous system vascular accidents.

The treatment consists of bed rest, sedation and the use of Dramamine or a similar drug during the acute stage of the dizziness, followed by the appropriate medical management of the cardiovascular disease.

Dizziness frequently occurs in patients with a hypotensive state and it is usually of postural type. The use of drugs such as ephedrine or ergotrate may be of some value in such patients.

Dizziness is not an uncommon complication at the menopause. Intermittent periods of postural vertigo may occur for one to two years. Hormonal therapy has been used in such cases but with indefinite results. The prognosis is good for complete relief from symptoms.

Certain drugs can cause dizziness and this is frequently a postural symptom only.

Another group of patients who often complain of dizziness are those with injury to the head. A high proportion of persons following a blow to the head may complain of dizziness for several weeks or months. The blow may not be severe enough to cause fracture or even unconsciousness. Usually such patients are dizzy only when they get into certain positions.

The practical importance of postural vertigo is not that it necessarily localizes the lesion, but that if this type of vertigo is indicated by a careful history it is usually possible to reproduce the symptom on postural tests and obtain objective proof by observation of the accompanying nystagmus.

The origin of dizziness following a blow to the head is not certain, but is not of practical importance since the dizziness subsides in time.

There are many cases in which no definite cause of dizziness can be determined. In some cases there may be a single short attack; in others, repeated attacks; and in many cases dizziness may be a purely postural symptom. The latter sometimes lasts for months and does not respond well to treatment. Avoidance of the offending positions is essential.

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The Pathogenesis of Peptic Ulcer

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• Peptic ulcers of the stomach and duodenum look much alike and the reaction around them is nonspecific, yet other evidence indicates that ulcers in the two locations do not represent the same disease. It is suggested that a common causal factor is the digestive effect of gastric juice, and that hypersecretion may produce duodenal ulcer without any predisposing change in the relatively susceptible duodenum. The development of a gastric ulcer, which may occur without hypersecretion, presumably requires some previous alteration of the normally resistant gastric mucosa. Focal metaplasia of the gastric mucosa to tissue resembling the lining of the small intestine, which is observed frequently in association with gastric ulcer, may be a factor in providing decreased resistance to peptic injury.

THE TERM "PEPTIC ULCER," in use since 1882, and applied to ulcers that occur in various regions of the alimentary tract reached by gastric juice, implies a common cause related to peptic activity. Most discussions make no clear etiologic distinctions between gastric and duodenal ulcers. The most recent edition of one of the commonly used textbooks of pathology[1] contains the statement that these two lesions "in all likelihood have a similar etiology."

The tissue reaction around peptic ulcers is nonspecific. There is fibrosis at the base related to the duration of the lesions, but no clues concerning pathogenesis are provided by the structure. This presentation will consider evidence of other sorts relating to ulcer pathogenesis, particularly with respect to the role of digestion by gastric juice and to the question of whether gastric and duodenal ulcer represent the same disease.

There is much evidence to support the dictum expressed by Schwartz[10] in 1910, which can be translated as "no acid, no ulcer." The absence of peptic ulcer in patients with pernicious anemia is striking. No report could be found of either gastric or duodenal ulcer in association with this disease where gastric achylia was present, and the author has never observed either type of ulcer when there were no parietal cells. The well-known occurrence of jejunal ulcer after gastroenterostomy in man or following the Mann-Williamson procedure in dogs, and the development of entirely comparable ulcers adjacent to Meckel's diverticula containing gastric mucosa provide strong evidence for a role of gastric juice in the production of these intestinal ulcers. Wells and MacPhee[12] recently emphasized the inverse relationship of the incidence of postoperative jejunal ulcer to the amount of gastric mucosa removed by the surgeon.

Of note also is the relatively recent observation that the administration of cortisone or corticotropin (ACTH) may induce peptic ulcer at the same time as gastric secretion is augmented.[6]

To these experiences may be added the frequent and predictable appearance of ulcers in animals treated with continuously acting histamine[11] and the regular occurrence of duodenal ulcers in dogs given continuous administration of 0.2 per cent pepsin in 0.15 normal hydrochloric acid by gastrostomy for several days.[5] This concentration of acid approximates the maximum which can be secreted by the gastric mucosa.

In relation to the possible role of acid and pepsin in the production of ulcers it is important to keep in mind not only the capacity of the mucosa to produce digestive secretions, but also the mechanisms which may inhibit their effect. Chief among these is the buffering influence of food, which may be sufficient to neutralize the free acid in the stomach completely. Hay, Varco, Code and Wangensteen[7] showed that proper feeding of animals may prevent the development of ulcer after histamine treatment, and like phenomena were observed by the author in similar experiments. Differences in eating habits, then, particularly in individuals with gastric hypersecretion, should be expected to produce considerable differences in exposure of the mucosa to active gastric juice. It seems probable that the development of peptic ulcers following severe burns, cerebral operations and head injuries may be prominently influenced by lack of protective food in the stomach of the acutely ill patients.

Alkaline duodenal content may be regurgitated into the stomach, and although this mechanism is unpredictable, it is a potential reducing influence upon the digestive activity of the stomach content.

From the Department of Pathology, Stanford University School of Medicine, San Francisco.

Presented as part of a Symposium on Peptic Ulcer before a Joint Meeting of the Sections on General Medicine and General Surgery at the 84th Annual Session of the California Medical Association, San Francisco, May 1-4, 1955.

The foregoing observations suggest an essential role of active gastric juice in the pathogenesis of gastric and duodenal ulcer in man, but there are several reasons for doubting that this is the only factor, or that it is even the major cause in some cases. Among these are some facts which suggest that gastric and duodenal ulcer may be distinctly different processes.

First is the different secretory pattern in patients with the different lesions. Many reports indicate hypersecretion in stomachs of patients with duodenal ulcer but not in those with gastric ulcer. This difference is particularly easy to recognize when the "basal" secretory activity is measured, as Bloomfield and French[2] demonstrated in 1938. This basal secretion is that which occurs without specific stimulation and so is particularly important because it represents the gastric secretion at a time when no buffering food is present in the stomach.

This difference of gastric function in patients with gastric and duodenal ulcer is paralleled by differences in stomach size. It was reported recently[3] that stomachs from patients with duodenal ulcer are nearly always larger than average and have a larger amount of acid and pepsin-secreting mucosa, while those from patients with gastric ulcer do not have these peculiarities.

Another anatomical difference in the two types of cases relates to the nature of the so-called chronic gastritis which is present. In nearly all cases of both types of ulcer there is infiltration of the gastric mucosa in the pyloric zone, or antrum, by plasma cells and lymphocytes, and this relation of ulcer to chronic gastritis has been noted repeatedly in the literature. Little attempt has been made, however, to differentiate between mucosal changes in gastric and duodenal ulcer cases. It has been suggested[4] that focal gastric mucosal metaplasia to glands of intestinal type may have a significance different from that of other changes which are included under the name of gastritis. This replacement mucosa is characterized by the presence of Paneth cells, inhabitants of normal intestinal mucosa, which are not seen in the normal stomach. In a comparative study it was noted that the incidence of metaplasia of this type in the gastric antrum was twice as frequent in cases of gastric ulcer as in controls or in association with duodenal ulcer (Table 1). The specimens bearing these ulcers were obtained at autopsy soon after death and were examined carefully in comparison with control cases of similar age and sex, factors which relate to the occurrence of gastric mucosal metaplasia.

Most of the metaplasia was situated at a distance from the ulcer; it was not simply a repair phenomenon at the ulcer margins. The possibility that it represents healed superficial ulcers in stomachs prone to development of ulcers has been suggested and cannot be certainly ruled out. In recognized healed ulcers, however, and at the borders of healing ulcers, the repaired mucosa has a different appearance, and does not assume the specific character of intestinal mucosa with recognizable Paneth cells.

TABLE 1.—*Frequency of focal gastric antral mucosal metaplasia in patients with chronic gastric and duodenal ulcer.*

	No. of Cases	No. with Metaplasia	Pct. with Metaplasia
Chronic gastric ulcer or scar	33	26	79
Matched controls	66	27	41
Chronic duodenal ulcer or scar	39	14	36
Matched controls	78	32	41

TABLE 2.—*Incidence of peptic ulcer in 3,400 autopsies.*

Location	Cases	Incidence (Per Cent)	Multiple Ulcers (Pct. of Ulcer Cases)	Combination of Locations (Pct. of Ulcer Cases)
Duodenum	122	3.6	34	11
Stomach	105	3.1	35	12

Ulcers of the stomach and duodenum might be expected to occur together as frequently as multiple ulcers appear in the same region if they are the product of the same causal factors. In a study of 3,400 autopsies on adult individuals performed over a ten-year period, multiple ulcers or ulcer scars in the same region (either stomach or duodenum) were found in about 35 per cent of the ulcer cases, while associated lesions in the two different regions occurred only one-third as frequently (Table 2). This incidence of associated gastric and duodenal ulcers is less than that which should exist if the same causes were involved in both.

These observations suggest fundamental differences in pathogenesis of gastric and duodenal ulcer and consequently indicate a need to consider the presence of factors other than digestive activity alone in the production of peptic ulcers. Such additional factors presumably modify mucosal resistance to peptic injury.

The normal stomach is quite resistant to acid and pepsin, as an essential feature of its digestive role. Deficiency in this resistance as a cause of ulcer is an old idea, and measured modifications in susceptibility to acid-pepsin injury have been produced in animals by various means. Among the mechanisms suspected as contributing to local reduction of mucosal resistance in man are vascular narrowing, ischemia due to shock, intoxications, irritation of foods, alterations in the surface protective layer of mucus, and vitamin deficiency. Clear proof of the influence of these or other possible mechanisms in the production of human peptic ulcer would be very difficult to identify since the operation of such factors might be transient or inconspicuous.

Recognizing that direct evaluation of factors such as these would be almost impossible in man, the author approached the question of whether some evidence of reduced resistance might be recognizable in the gastric mucosal structure. The change which presents itself as possibly providing this evidence is the focal mucosal metaplasia described above, which appears with unusual frequency in association with gastric ulcer and affects principally the pyloric zone, or antrum—the region in which practically all gastric ulcers are found.

It is possible that this altered mucosa of the intestinal type is itself less resistant to the action of gastric juice, in view of demonstrations that intestinal mucosa in animals is more susceptible than gastric mucosa to injury by the elements of gastric juice.[8, 9] A greater susceptibility of intestinal mucosa to peptic injury would provide an explanation for the predominance of ulcers in the duodenum when no gastric mucosal metaplasia is present, and it is tempting to suspect that gastric mucosal metaplasia might represent a reason for the development of comparable ulcers in the stomach even in the presence of relatively low gastric secretory activity. Inasmuch as metaplastic change could be regarded only as a predisposing cause, the lack of better correlation with the occurrence of gastric ulcer can be explained, and the author believes that the possibility of a predisposing role of mucosal metaplasia of the intestinal type should not be neglected. It is possible that a metaplastic alteration which is not distinctly recognizable as intestinal mucosa might also represent decreased resistance of the gastric mucosa.

CONCLUSION

The observations herein outlined represent an incomplete survey of the large number of studies which bear upon the ulcer problem, but they point to certain suggestions concerning the pathogenesis of peptic ulcer which can be expressed in the following hypothesis: The destructive mechanism which produces peptic ulcer is peptic digestion in an acid medium. This may require little predisposing change in the relatively susceptible jejunal mucosa after gastroenterostomy, in the mucosa of the ileum adjacent to a secreting Meckel's diverticulum, or in the duodenum when gastric secretory activity is high and there is inadequate neutralization of the gastric juice. The normal stomach, by contrast, is resistant to gastric juice even when it is concentrated. If acid and pepsin concentrations are low, the duodenal mucosa also resists injury; but even with a reduced secretory capacity of the stomach, abnormalities in its antral portion, perhaps represented by the intestinal type of mucosal metaplasia, may provide sufficient reduction in resistance of this region to permit development of gastric ulcer.

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The Management of Peptic Ulcer

An Internist's Approach

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• Gastric and duodenal ulcers are common conditions. There is a good natural tendency to heal but medical care does facilitate healing and the prevention of relapse. Bed rest, light diet and attention to the anxiety factor still pay dividends. Unfortunately there have not been any major medical advances in recent years.

With gastric ulcer, careful clinical and radiological observations will enable simple and malignant ulcers to be distinguished with considerable accuracy.

The risk of gastrectomy is less than the risk of leaving a persistently unhealed ulcer, and should be undertaken if ulcers remain unhealed or if there are frequent relapses threatening economic security.

IT IS IMPORTANT to have some perspective of the problem of peptic ulcer as it occurs in the community and particularly to remember that the scars of gastric and duodenal ulcers are one of the commonest of incidental observations at autopsy. There is undoubtedly a very good natural tendency to recovery and there is no doubt that medical treatment not infrequently gets the credit for nature's cure. Taking the total number of persons with diagnosed ulcers in the community—those who have had definite ulcer-like symptoms or complication of ulcer—it will be noted that in about one-third of the cases, the ulcer has been an episode followed by some years of freedom from dyspepsia, or with perhaps slight symptoms; and that in rather more than one-third of the patients there are recurrent symptoms at varying intervals but that with some degree of care and discretion the bouts of dyspepsia can be minimized and lead to little or no loss of time from work. In the remaining cases, the patient has had a great deal of pain or troublesome complications and if operation has not already been performed, it is really needed. This is the picture that one gets when a total population is surveyed, as I had the opportunity of doing with Dr. Doll a few years ago, when we interviewed about 6,000 people in a variety of occupations. Those who work only in hospitals might perhaps feel that the overall picture of ulcer is much more troublesome, but of course the patients are already a selected group by the time they reach hospital.

In terms of pathology, the natural history of ulceration in the more troublesome cases is a whole series of ulcers which come and are healed completely, but a time may come when the ulcer no longer heals and with increasing induration and endarteritis of the smaller blood vessels, the blood supply becomes so deficient that it can no longer sustain healing tissue and in fact healing is no longer possible. At this stage, the ulceration process can always flare up, causing further penetration and erosion of main blood vessels, but sometimes these persistent chronic ulcers may be remarkably pain-free for many months on end. Obviously at this stage surgical treatment is required.

The size of the ulcer does not correlate well with the amount of trouble caused to the patient. Some of the most persistent and painful ulcers are relatively small. On the other hand, a very large ulcer with a short history may heal completely and remain healed.

An accurate diagnosis is of course the first essential. It is perhaps not sufficiently realized how atypical the pain may be. It is easy enough with remittent attacks of epigastric or retrosternal pain related to meals, but quite often the pain bears no relationship to food and its site may be unusual—in the lower chest, the loin, the back or the iliac fossa. Sometimes pain may be felt in the back only. Again, pain may be virtually absent, but with perhaps only a sense of discomfort or nausea; and there seems no doubt that the ability of some patients to feel deep-seated pain varies greatly and it may be possible to correlate this with an obvious depression of deep-pressure pain when tested by pressure on the styloid process or the Achilles tendon. These cases are only diagnosed when the internist is prepared to order a barium meal with these atypical clinical pictures.

We have no specific treatment for peptic ulcer, and I do not believe there have been any specific

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cures in spite of many claims made in recent years. The management of peptic ulcer is still an exercise in old-fashioned medicine just as was pneumonia before the introduction of antibiotics. Nevertheless, a great deal can be done to influence the disease process. The essence of treatment is achieving physical and mental rest, and the relief of pain. From the patient's point of view the relief of pain is the first essential. Bed rest and small feeds may be sufficient with alkalies, milk drip and anticholinergic drugs in reserve. The best single therapeutic measure for troublesome pain is a milk drip, and a very small intranasal tube is well tolerated by the majority of patients. If relief of pain is slow and difficult to achieve it is of bad prognostic significance and operation is generally required. Having achieved relief of pain one can then concentrate on the general measures, particularly those which influence the disease process. I am sure bed rest is one of the most important therapeutic measures. My colleague, Dr. Doll, has measured the rate of healing of gastric ulcer, and has observed the influence of antacids, belladonna, phenobarbitone, Robaden and milk drip, but so far a significant improvement can be correlated only with bed rest. However, in individual circumstances it may be better to let the patient carry on at work rather than impose the added financial hardship of loss of employment. Patients who put on weight usually do well and patients who lose weight do badly. The basic diet should be built up as quickly as possible to provide an adequate calorie, protein and vitamin intake, and the milk drip kept going for a time to further improve the nutritional state.

The next essential is to tackle the anxiety factor which may seriously aggravate the disease process and retard healing. It is important to establish good rapport with the patient, and this needs time, privacy and patience, and on the whole is more easily done with a patient having bed rest than attending one's consulting rooms. Once the patient feels he has a sympathetic independent person who is anxious to help and is there in the capacity of friend and not as judge, he may be prepared to unburden his difficulties which too often have caused pent-up emotional stress because there has been no one in whom he can confide. The relief of such emotional tension is in itself of great therapeutic value.

So often the patient gets his difficulties out of perspective and they have become much more important than they really are. This is where the independent observer can so well help. This approach is equally important with other chronic illnesses such as pulmonary tuberculosis and skin disease. I prefer to call this not psychosomatic therapy but ordinary old-fashioned medical care. It was certainly instilled into me by Professor Frazer at St. Bartholomew's Hospital long before psychosomatic medicine was talked of.

As far as diet is concerned, I believe a simple commonsense diet avoiding the common indigestible foods, with regular feeds is all that is necessary. I do not advocate elaborate dietary regimens. One should always avoid overtreatment, which can be positively harmful with a patient of obsessional type.

With regard to medication, I hold no brief for excessive and persistent use of alkalies, apart from the initial phase when there is pain. Alkaline therapy is, however, usually necessary with ambulatory treatment. There is no doubt that excessive milk and excessive alkalies can lead to metabolic difficulties and chronic tubular nephrosis. I believe the most important single medication in the management of peptic ulcer is phenobarbitone. I do not hold any strong brief for the use of anticholinergic drugs except when there is pain. During the past few years there has been a tremendous spate of these anticholinergic drugs. Belladonna has had a time honored role, and these new preparations have sought to emulate its action, but with fewer undesirable side-effects. Banthine® blazed the trail and has been followed by a bewildering number of other drugs, including Antrenyl,® Bentyl,® Centrine,® Lergine,® Lytensium,® Monodral,® Pamine,® Prantal® and Wyovin®; and much has been written on both sides of the Atlantic about their pharmacological and clinical effects.

All these drugs have much in common. The chemical composition is complex; they achieve an anticholinergic effect like atropine, either by blocking transmission at autonomic ganglia or at the peripheral effector site; they reduce basal secretion and slow the emptying time of the stomach and reduce intestinal muscular activity. Although it is mainly claimed that side-effects are minimal, in practice the usual atropine-like disturbances of impaired vision and dryness of the mouth, are quite common and sometimes there may be difficulty in urination and constipation. Moreover, there is considerable variability in response between different patients and even in the same patient at different times.

In general the therapeutic contribution of these new drugs is not impressive and they do not represent any real major advance in the therapy of peptic ulcer. Nor were they likely to do so, as atropine and related drugs, although of real value in smooth muscle spasm, have never been conclusively proved to be of great worth in the management of peptic ulcer. Most clinicians would agree, however, that belladonna can be useful in stopping pain, particularly night pain, in duodenal ulcer. According to Nicol[2] (1939), even really large doses of atropine apparently had very little effect on the

acid of the stomach when measured over 24 hours and no better success seems to have been achieved by ganglion-blocking agents in this respect (Rowlands,[3] 1952). It has been postulated that slowing the rate of emptying of the stomach would allow the more effective use of antacids, but this hypothesis is by no means proved. The distention of the stomach is itself an important stimulus to secretion, and slowing of the rate of emptying may well mean more prolonged secretion, which would offset the neutralization. Again the inhibition of other intestinal secretions, particularly pancreatic, might offset any benefit to the duodenum from lowering of the gastric acidity. Indeed, as a means of facilitating healing of peptic ulcer, the use of these drugs is still based on doubtful hypotheses and insufficient clinical study with control series.

The clinical evidence of the value of methantheline (Banthine) in controlled observations was quite unimpressive apart from some reduction of pain, and Friedlander[1] (1954) did not find that the natural history of duodenal ulcer was beneficially affected. Texter and Barborka[4] (1954) followed 250 patients with proved peptic ulcer for two years. They concluded that although symptomatic improvement for a period frequently accompanied the use of these agents, the eventual course of the disease was not altered.

Although the natural history of the disease is not materially influenced, improved relief of pain is an important consideration from the patient's point of view and justifies the use of any of these preparations during the phase of active ulceration, but it would seem reasonable to see whether the desired effect cannot be obtained with the traditional belladonna, before prescribing these new, and much more expensive, preparations.

In general, patients like to have brand new treatments and it is an advantage to have a variety of compounds available in the management of a chronic and relapsing disease. Apart from some difference in side-effects, it is unlikely that any one of the many new preparations will prove to have any real superiority over its rivals, and the practitioner need not feel that he must personally evaluate each preparation.

What can be done about the prevention of relapses? One should aim at the prevention of nervous tension, of fatigue, of irregularity of meals, of long intervals without food, and at the maintenance of a good nutritional state. Prevention of fatigue usually means giving up some commitments, and the physician must take full advantage of the period of illness to encourage the patient to lighten his load, which he can do on medical grounds without loss of face—a most important consideration, as otherwise he feels that his colleagues think that he is letting the side down, and this engenders more tension. I believe the patient can do a great deal to reduce his state of chronic nervous tension once the problem is posed to him. It is possible for a patient to get out of his skin and look at himself, and really ask what he is gaining by his constant state of nervous anticipation. To a certain extent it may have become a bad habit which by voluntary effort the patient may be able to overcome with encouragement and assistance. Finding some new form of relaxation is most helpful, particularly, music, painting or some contact with the countryside — bird watching or the study of trees and flowers. A wider vista of life in other forms does much to help the individual to get his own life and little problems in proper perspective. Sometimes breathing or postural exercises have a remarkable effect in enabling the patient to reduce his emotional load. I have seen many patients who have been able to overcome their chronic anxiety state.

The internist has an important role in the selection of patients for operation. With good selection, excellent results are obtained in about 85 per cent of cases, poor results in 5 per cent, with a 1 to 2 per cent mortality rate. However, one is still a bit concerned about the long-term follow-up—about a tendency to weight loss and anemia, and tuberculosis—and it is wise to ensure that the patient "earns" gastrectomy by evidence of failure to respond to medical management or by troublesome relapses.

The foregoing are general considerations, and I would now like to turn to particular problems of management of gastric and duodenal ulcer separately.

Gastric Ulcer

First, it is important to realize that radiographic studies can be misleading. Small gastric ulcers are not always visualized radiologically and may be seen gastroscopically, but false positive diagnoses are not infrequent, and rugal folds particularly high up on the lesser curve may simulate a gastric ulcer. Further diagnostic difficulty may sometimes arise with hyperperistalsis and with primary gastric diverticulum, and gastroscopy is very helpful particularly when there is some discrepancy between clinical and radiological pictures. Figure 1 illustrates pseudo ulcer.

Naturally, with gastric ulcer the question of malignancy arises, but I believe that with a combination of radiological and gastroscopic studies it is possible very accurately to pick out simple ulcers. Our confidence in so doing has been strengthened by a follow-up study of 285 consecutive patients with gastric ulcer, followed up over three years. The

Figure 1.—A pseudogastric ulcer due to rugal irregularities.

TABLE 1.—*Differential diagnosis of simple ulcer.*

Material: All fresh cases of gastric ulcer—i.e., cases never previously diagnosed at Central Middlesex Hospital or elsewhere—seen at the hospital over a period of two years.

Total	307
Initially diagnosed at partial gastrectomy for perforation or hematemesis	22
Available for study	285

Clinical Group	No. of Cases	Presumed Benign Ulcer (Incomplete Follow-up)	"Proved" Benign Ulcer	"Proved" Malignant Ulcer*
I	266	16	249	1 (0.4%)
II	19	0	15	4 (21%)
Total	285	16	264	5 (1.8%)

Notes:

Group I—Confident diagnosis of benign ulcer x-ray studies available	255
Diagnosed at operation for perforation only	3
Diagnosed at gastroscopy only	8
Group II—Diagnosis of benign ulcer, but possibility of error recognized	19

Proof of benign ulcer:

Group I—Died, no evidence of gastric cancer	12
Subsequent partial gastrectomy	64
Followed for 3 years; no evidence of gastric cancer	173
Group II—Died, no evidence of gastric cancer	1
Subsequent partial gastrectomy	6
Followed for 3 years; no evidence of gastric cancer	8

*Proof of malignant ulcer by autopsy or by partial gastrectomy in each case.

ulcers were put into two groups—those thought to be simple and those in which there was an element of doubt. Ulcers thought to be definitely or probably neoplastic were classified separately and treated surgically.

The follow-up is, in fact, not yet complete but amongst the ulcers deemed to be simple only one was proved malignant in our follow-up studies.

The distinction between simple and malignant ulcer of the stomach is most important. With the combination of clinical features and radiological findings and, in doubtful cases, gastroscopy, it is possible to achieve a very high degree of accuracy. (From the follow-up experience it seems that the chance of missing a malignant ulcer is less than one-half of 1 per cent.) But this can be achieved only by constant vigilance and cooperation between the radiologist and the clinicians. My colleague, Dr. Pygott, radiologist at the Central Middlesex Hospital, stresses the following points between the diagnosis of simple and malignant ulcer:

(a) *Size and site.* Mere size of the ulcer is not of any diagnostic significance, nor is site in itself an absolute criterion, but simple ulcers of large size are rare in the antrum and on or near the greater curvature.

(b) *Shape.* Ulcers that form a saddle across the lesser curvature extending out to both anterior and posterior walls of the stomach are usually malignant.

(c) *Character of the crater.* Simple ulcers occurring anywhere except in the roof of the antrum near the pylorus can generally be shown in one view or another to project beyond the general outline of the adjacent normal portion of the stomach. Where a large part of the stomach wall is occupied by an ulcer so that the profile features are indeterminate, some help may be obtained from the fact that large neoplastic ulcers tend to be relatively shallow whereas large simple ulcers are usually deep. As a side feature, air is rarely trapped in the crater of a neoplastic ulcer in the standing position but is commonly trapped in large simple ulcers.

(d) *Margins of the crater.* The margins of a neoplastic ulcer may be quite shallow and irregular when ulceration has just commenced in a plaque of growth. The meniscus sign of a rolled margin to the ulcer is equally well seen in large simple ulcers as in neoplastic ones and is not, in my view, a deciding one—except when it is found around a shallow ulcer, when I believe it can be a useful sign of neoplasm.

(e) *Features of the surrounding stomach.* Gross distortions of the normal outline of the stomach can occur as a result of simple ulceration through scarring in the ulcer area and extending from it. These distortions are of a linear character—i.e., pulling

Figure 2.—A simple gastric ulcer showing the ulcer projecting clearly from the lesser curve.

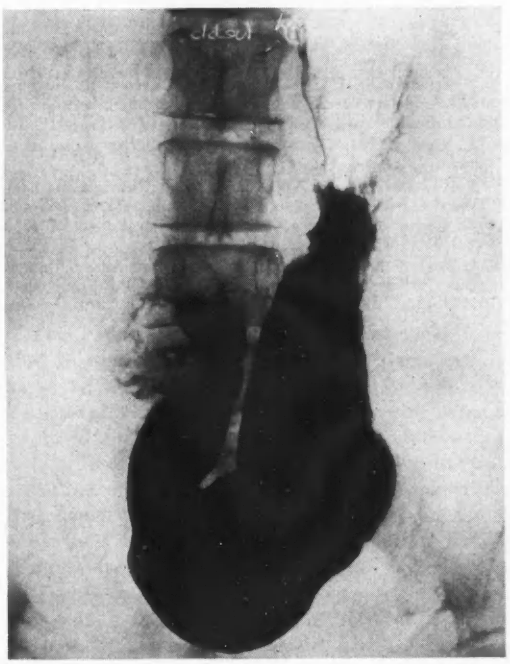

Figure 3.—A malignant ulcer of the stomach showing the ulcer crater is within the line of the lesser curve.

TABLE 2.—*146 patients with gastric ulcer treated in bed for four weeks.*

	No.	Per Cent
Completely healed	34	23
More than 80 per cent healed	32	22
50-79 per cent healed	40	27
Less than 50 per cent healed (including 14-10 per cent with ulcer larger than on admission)	40	27

All followed up. None had cancer.

toward the ulcer or ulcer site in radiating lines from it—commonly in the line of the lesser curve itself, rolling the stomach up and drawing up the antrum and pylorus; or obliquely down into the antrum, resulting in the teapot type of deformity; or transversely, resulting in the hourglass deformity, the greater curve being drawn toward the lesser.

In neoplastic ulceration, deformity of outlines tends to be multidirectional. The antrum may be generally contracted in a more or less conical manner, or the curvatures of the stomach may be irregularly approximated from the two sides or a smaller area of stomach may be bizarre in shape.

The mucosal pattern around the neoplastic ulcer may of course be grossly destroyed or the rugae may be stiffened and broadened and little affected by controlled compression.

Reference is always made to disturbances of peristalsis in the area of ulceration, but this is of relatively slight value in the cases presenting most difficulty. Contractions are grossly impaired or absent in the vicinity of large simple ulcers. Of course, where peristalsis is absent in an area of the body of the antrum where ulceration is slight in extent, there is good evidence of neoplastic involvement.

At times gastric insufflation through a Ryle's tube with air either alone or in combination with intravenous injection of morphine, 6.0 mg., may give more clearly defined answers to the points raised but these special methods do not supplant an investigation by a complete routine which should include careful palpation of the abdomen when an ulcer of doubtful nature has been located.

It is in fact easier to distinguish between simple and malignant ulcers radiologically than it is to distinguish them from the peritoneal surface at a time of acute perforation, and in our experience some 10 per cent of "simple gastric ulcers" diagnosed at laparotomy for perforated ulcer, are in fact malignant. Gastroscopy is, of course, a further aid in achieving accuracy of diagnosis (see Figure 4).

There is no doubt that in patients with a gastric ulcer with a short history, complete healing often occurs. In fact, this may occur while they are on a waiting list to come into hospital. Once they come into hospital our general experience with the healing of gastric ulcer is summarized in Table 2.

Figure 4.—A malignant ulcer in the pyloric antrum which appeared to be a simple ulcer from the peritoneal surface at the time of acute perforation.

Surgical treatment is not generally undertaken unless after some months the ulcer still remains unhealed with return of symptoms. I do not believe that routine partial gastrectomy is needed for all gastric ulcers. If one can achieve complete healing radiologically and gastroscopically, there is, in fact, a very fair chance of the patient's having some years of freedom from further trouble. In practice, about half the patients will need operation sooner or later.

Duodenal Ulcer

Although the radiological diagnosis of duodenal ulcer is fairly accurate, it is possible for patients to have troublesome and severe symptoms with a well filling duodenal cap which may hide an ulcer in the postbulbar region. Generally speaking, every patient with a duodenal ulcer should be given a thorough trial of medical treatment. With patients with more than a two-year history the chance of getting a prolonged remission is probably less than 10 per cent, but with a short history or with patients with long remissions and those with obvious environmental factors which can be influenced, medical treatment should certainly be continued. A bias toward surgical operation is needed for patients with unusually severe pain, and particularly pain in unusual sites—such as through to the back—when the pain does not readily respond to ordinary medical measures, and when the complications of hemorrhage, perforation or stenosis have arisen. The combination of gastric and duodenal ulcer is also a further argument for operation.

Stomal Ulcer

The medical dividends are small but they do exist particularly when there has been some exogenous factor leading up to the breakdown, but in most cases partial gastrectomy or further partial gastrectomy with vagotomy is indicated, and, if ulceration then recurs, total gastrectomy.

The internist can play an important role, not only in medical management but also when operation is needed. All the surgical patients remain in my medical wards for their operation, and I assist in the prevention and control of respiratory infections and postoperative complications, and the maintenance of proper blood and electrolytic balances.

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Gastric and Duodenal Ulcer

The Surgeon's Approach

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• *A surgeon must have a clear conception of the indications for operation for either gastric or duodenal ulcer. He must realize that his indications must be modified by his operative mortality. The operation he carries out must be determined by several factors. It is the author's opinion that the various types of distal partial gastrectomy are those most likely to succeed and to produce the fewest undesirable postoperative sequelae.*

GASTRIC AND DUODENAL ULCER are entities which deserve separate consideration. Since a greater measure of disagreement attends the management of gastric ulcer, this type will be considered first.

It always has been a source of amazement that the methods of therapy in gastric ulcer can vary so widely, as described by various authorities throughout the country. This, if nothing else, proves that there is no fully accepted method, and that any statements—including this one—represent personal opinions. As a corollary it should be stated that such opinions throughout the country will vary, depending upon the relative abilities of the various members of the diagnostic and therapeutic team. This team must include gastroenterologist, radiologist, endoscopist, cytologist, anesthesiologist and surgeon. In centers where one of this group is dominant, the therapy of gastric ulcer is liable to become colored significantly by his opinion.

The surgeon's point of view of the therapy of gastric ulcer usually is extremely simple and probably is shared by most surgeons in this country. He believes that medical therapy of gastric ulcers is unsatisfactory except for the small proportion that are acute and heal rapidly under observation. Approximately 75 per cent are chronic or heal slowly or not at all, in a period of hospitalization. They should be treated by subtotal gastrectomy which not only promises a definitive cure of the ulcer if it is benign, but gives the only chance of cure if it is malignant.

This rather simple statement requires amplification in many respects. If it is to be accepted, it must be assumed that the operative mortality is considerably lower than the number of patients operated upon who actually have cancer rather than benign ulcer, for in only about half of the cases of cancer treated in this fashion will the patients survive five years. Furthermore, postgastrectomy symptoms must be infrequent, so that very few gastric cripples are produced.

These considerations apply to approximately 95 per cent of the cases in which the ulcer is in the distal portion of the stomach. Ulcers there can be excised by subtotal gastrectomy that is associated with a mortality of 1 to 2 per cent and with almost complete absence of postgastrectomy symptoms. Only rarely does an anastomotic ulcer develop later. All follow-up statistics to date have shown that postoperative results are excellent in 90 to 95 per cent of this group, which is significantly higher than for duodenal ulcers.

However, the 5 per cent of all gastric ulcers that originate in the juxta-esophageal area pose different problems. Here the operative mortality is higher and, if resection should involve a very high subtotal gastrectomy or total gastrectomy, the postoperative sequelae are liable to be very severe. Consequently ulcers in this area logically may be treated in a more conservative fashion. If all studies indicate the ulcer is benign, including cytological smears and gastroscopic biopsy, four to six weeks may be allowed for healing.

When the usual gastric ulcer is considered, operation is carried out at once if there is a history of chronicity or any concomitant complications such as severe hemorrhage, obstruction, penetration or perforation. For example, pain felt in the high lumbar area of the back, in the presence of a gastric ulcer, is usually due to penetration into the pancreatic capsule and should be treated by operation. In the case of the rare gastric ulcer that is entirely asymptomatic and is diagnosed for the first time by x-ray examination, operation should be done at once because of the chances of malignant disease. Ulceration, in the presence of complete histamine achlorhydria, also indicates operation, as does any

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gastric defect in a patient with pernicious anemia.

In the remaining cases there is a short history, usually of pain alone. The patients should be hospitalized and treated vigorously by a gastroenterologist. Cytologic studies and gastroscopy must be done and any evidence of cancer demands immediate operation. If such evidence is not present, operation should still be carried out unless significant progress toward healing is observed at a second examination 10 to 14 days later. If the ulcer heals completely in four to six weeks of conservative therapy, follow-up examinations are mandatory and any recurrence should be treated by operation.

CHOOSING THE OPERATION

The surgeon, then, should bear the responsibility of the treatment of about three-quarters of all cases of gastric ulcer. Let us assume then that operation is being carried out for a gastric ulcer and according to all methods of study it is benign. How shall he conduct the operation?

Here again it is wiser to divide cases into two groups, those in which the position of the ulcer indicates it can be treated by distal partial gastrectomy, and those in which the lesion is juxta-esophageal. As to ulcers in the distal stomach, it might be recalled that several years ago it was said that an operation for gastric ulcer should be the same as that for gastric cancer. Since that time so many radical and even preposterous operations for cancer of the stomach have been proposed, that this old statement is meaningless. A more exact description now is necessary. If the ulcer has not penetrated the wall of the stomach, subtotal gastrectomy should be carried out, removing the lymph nodes along both curvatures, and the greater and lesser omentum. While a margin of 5 cm. above the ulcer is desirable, it is not essential.

The stomach, however, is divided with the actual cautery. The resected stomach should then be examined by a pathologist by a frozen section if possible. In this way, in the very unusual case in which cancer is found and an insufficient amount of gastric wall has been removed, a higher resection is carried out and the anastomosis completed.

Not infrequently the ulcer will have perforated onto the body or tail of the pancreas. Here the surgeon may prefer to open the stomach, inspect the lesion within, take a specimen for biopsy and be guided in the extent of the resection by the pathologist's report. In case of doubt, it is advisable to adopt a conservative approach. Cancer of the stomach that involves the pancreas is practically never cured. On the other hand, to resect a portion of the pancreas in a case of benign ulcer may result in the death of the patient or in difficult convalescence when otherwise there might have been prompt recovery.

As to ulcers in the juxta-esophageal area, opinions are in a state of flux. Let us assume again that all preoperative studies have indicated a benign ulcer. Some years ago it appeared that the answer to this problem would be a proximal partial gastrectomy. This necessarily involved bilateral vagotomy, resection of the cardia and anastomosis of the esophagus to the antrum of the stomach. The end results of this operation as performed in the Massachusetts General Hospital for benign ulcer were presented recently by Sweet.[13] They indicate, just as do other reports from different sections of the country, that the mortality is relatively high and that postresection symptoms are not uncommon.

Recourse therefore should be had to a different type of operation, and the best one at present appears to be that described by Madlener.[9] Here the high gastric ulcer is not removed, but a distal subtotal gastrectomy is carried out. Healing results later because the gastric antrum and much of the acid-secreting area have been removed. This operation has given uniformly good results when it has been done for ulcer according to Maurer[10] and Colp,[5] each of whom has reported a significant number. It obviously has given uniformly bad results when it has been carried out for cancer; hence, intragastric biopsy and frozen section should be employed in every case in which this operation is used. Postoperatively careful x-ray examination and follow-up observation are necessary to be sure that the lesion heals.

DUODENAL ULCER

Duodenal ulcer poses a different problem than gastric ulcer. Here there is some disagreement among physicians and surgeons about the patients who require operation. There is even more internecine warfare among surgeons about the selection of the type of the operation that is to be carried out.

It is not easy to deal succinctly with the various indications for operation for duodenal ulcer. The problem is simplified if discussion of the emergency operations for suture of perforations is omitted and consideration is given only to operations performed for definitive cure of the ulcer. Attention should be called again to the very complete and important study carried out by Moore[11] and associates at Massachusetts General Hospital a few years ago. Every patient who entered the ward service between 1942 and 1946 was followed carefully up to mid-1949. It was found that the mortality rate of those treated by subtotal gastrectomy was 2.86 per cent. This was an operative mortality and occurred at once. The mortality rate of those treated conservatively, surprisingly enough, showed no significant

difference, but was due to the complications of ulcer spread over a five-year period. Meanwhile, those treated by subtotal gastrectomy were, except for a very small percentage, asymptomatic, leading active lives; of those treated conservatively, about three times as many had an unsatisfactory result in symptomatic or economic terms. Moore and associates then attempted to define the patient with "virulent" ulcer, who ought to have operation without delay. It is possible to pick out, by their definition, many patients who should have operation but are limping along on a conservative regimen, living for their ulcers, rather than leading normal lives.

In brief it seems logical that patients with a duodenal ulcer who fall within any of the following categories should have a definitive operation for cure unless operation is contraindicated by other considerations: (1) Those who have had a perforation and a prolonged period of ulcer symptoms before or after the perforation. (2) Those who have had an attack of obstruction or in whom severe deformity of the duodenum is observed roentgenographically. (3) Those who have had a single massive hemorrhage or two or more moderate ones. (4) Those who have had to be hospitalized two or more times for the treatment of pain, or who continue to suffer despite careful attention to a gastroenterologist's advice. It is also of interest that in the previously mentioned report by Moore and coworkers, it was noted that persons in whom ulcer symptoms developed before the age of 20 or after the age of 70 also usually had "virulent" ulcers.

From these indications it is apparent that many more patients with ulcer should be operated on without delay, yet many physicians, and surgeons as well, are a little more conservative in their approach. There are many patients who, on the appearance of the first symptoms of ulcer, rush to a surgeon. It would seem a good general rule that for such patients operation should usually be avoided, for they vision operation as an immediate escape from their underlying difficulties and assume that once they have recovered from the operation they will be normal again. They will be sadly disillusioned. In general terms a patient should be made to understand his ulcer diathesis and learn how to treat it before operation is carried out. It might be stated parenthetically that a certain period of suffering before operation results in much more gratitude to the surgeon and fewer complaints after the operation.

One must not forget that an ulcer is merely an accompanying finding in many patients with psychoneurosis or, as Sarah Jordan has said, the patient is intractable, rather than the ulcer. Although their complaints may be epigastric, proper surgical treatment for ulcer will not cure them. Whenever compensation neurosis is suspected, the surgeon should not be too aggressive. A very interesting note in this regard was supplied by Carmody,[4] who reported that two patients with very severe symptoms from duodenal and anastomotic ulcers had lobotomy and the ulcers then healed rapidly.

SELECTING OPERATION FOR DUODENAL ULCER

Assuming that an operation is to be done, let us now consider the type of operation to be carried out. The surgical literature is now full of claims and counter-claims and several new operations are being tested. It is no wonder that young surgeons are confused completely as to the approach to any specific case.

To make the author's position clear at once, let it be noted that he is biased in his opinion, probably no more so than anyone else, but definitely biased. He believes a distal partial gastrectomy in which not over 75 per cent of the stomach is removed is a wonderfully effective operation. He recalls a host of unbelievably grateful patients. The words of an internist who has observed many of these patients for many years after operation sound more than faintly musical when he says that subtotal gastrectomy is the finest operation ever performed by the abdominal surgeon. He is sure that many of the complaints about the operation have been exaggerated. Every medical student can recite all the variations of the dumping syndrome, listing enough symptoms so that if they all were significant a good proportion of so-called normal persons must have the condition. The surgeon agrees that the patient who has had a subtotal gastrectomy and flushes after he has had a glass of chocolate milk, has a variant of a dumping syndrome; but the surgeon is not sure that it is important, particularly if the patient has been relieved of his serious symptoms—and does not like chocolate milk. The surgeon hears that his patients cannot gain weight after a gastrectomy, despite voracious appetites. As a philosopher he may look at his own expanding anatomy, view his innumerable obese patients who are condemned to live on salads and wonder which people are happiest.

On the other hand, even though the complaints about gastrectomy have been exaggerated, every surgeon will admit that there are a few patients who are unhappy after it. In a series of patients followed by the author several years ago, excellent or very satisfactory results were noted in approximately 88 per cent of those who had had this operation. Anastomotic ulcers developed in 3 per cent of the patients, 3 per cent had an attack of postoperative bleeding without known source and 3 per cent had severe weight loss or various troublesome digestive symptoms including the dumping syndrome. As

time went by the patients with digestive symptoms improved. For example, a woman who had been coached by her two physicians for nearly two years about the dumping syndrome before gastrectomy, took exactly two years to get over it following operation, and from then on she was entirely asymptomatic.

It is a personal opinion, and this is not susceptible of proof, that one of the reasons partial gastrectomy is regarded with disfavor in some quarters is that such radical resections have been performed in some localities that postgastrectomy symptoms have overshadowed the benefits of the operation. The greater the amount of stomach removed, the less is the chance of stomal ulcer, but also the greater the chance of postgastrectomy symptoms or severe weight loss. The surgeon must attempt to leave enough stomach to strike a balance; it is very rarely that over 75 per cent should be removed. It should be less if the patient is a woman, or one who has always been thin or who has a greatly distended stomach at the time of the operation. If symptoms are out of proportion to the amount of pathologic change demonstrated—as, for example, when very little deformity is shown by x-ray or at operation despite a history of many years — the resection should be more conservative.

NEW COMBINATIONS

The question then arises as to whether or not a more satisfactory operation than partial gastrectomy has been devised. Out of some fifteen operations that have at one time or other been used for ulcer, the greatest interest, of course, has attended the operation of vagotomy. The emphasis upon this operation has gradually shifted. Vagotomy alone soon was abandoned. The next modification was that of vagotomy and a short posterior gastroenterotomy. Because of Dragstedt's[6] enthusiasm, some surgeons still employ it. The author's results have not been good with either; results were unsatisfactory in 40 per cent of a series of 27 cases in which the operation was done in 1946 to 1947, so the operation was discontinued except for anastomotic ulcer. A recent follow-up observation of a patient typifies the reasons for this discouragement. Almost absolute atonicity of the stomach developed after vagotomy and posterior gastroenterostomy, and no acid secretion occurred after intravenous administration of insulin. Five years later the patient reentered the hospital with serious bleeding from a reactivated duodenal ulcer and the stomach contained 60 units of free acid after histamine was given. A recent complete follow-up of the entire Massachusetts General Hospital series of 132 cases by Brooks and Moore[3] led them to believe that the operation should be abandoned.

Most hopeful of the new operations is a combination of a relatively conservative resection with a vagotomy, as advocated by Smithwick.[7] He expressed the hope that it will combine the good features of both—that is, prevention of loss of weight and a reduction of the dumping syndrome. It is to be hoped that it will do that rather than combining the bad features, namely, the higher operative mortality of gastrectomy and the occasional persistent diarrhea following vagotomy. A few more years will be necessary to evaluate it as well as other operations being carried out in various sections of the country.

Harkins'[8] emphasis on extension of the Billroth I operation is very important, especially with regard to thin or female patients. It is certainly applicable to many gastric ulcers, but has not been accepted generally for duodenal ulcers. Wangensteen's operations that are designed to reduce the acid-secreting areas of the stomach, as well as other experimental procedures that are being carried out elsewhere, will be watched with great interest.

Theoretically, a combination of 75 per cent gastrectomy and vagotomy should provide the greatest protection against recurrence of ulcer. Several series of these operations have been compared with a central series in which the vagotomy had been omitted. A typical study was one reported by Palumbo.[12] He found that achlorhydria was produced regularly by the combined operation but that the persistent diarrhea that often followed vagotomy made its addition to subtotal resection questionable.

Meanwhile, the surgeon who wishes to use the best method to cure his patient of duodenal ulcer had better apply accepted techniques. Recently an eminent gastroenterologist characterized surgeons as the greatest faddists in the whole field of medicine. He is probably correct, and, for the moment, let us not be swept off our feet by all of these new developments. So many operations for duodenal ulcer have come and gone that some which now seem very attractive may be based on fancy rather than on fact. It may be that the surgeon who chooses partial gastrectomy—the same operation now that he did a decade ago—may not be doing so simply because he is so obtuse that he cannot see anything better. He may actually be a little closer to the answer.

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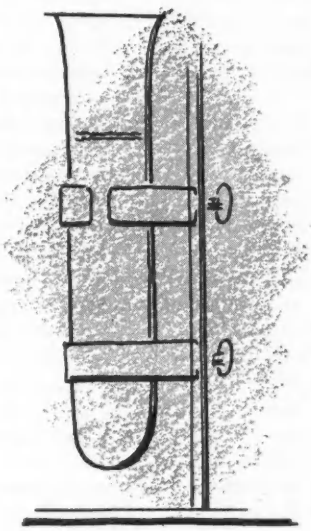

Megaloblastic Anemia

Associated with Surgically Produced Gastrointestinal Abnormalities

JAMES A. HALSTED, M.D., Syracuse, N. Y.

• Two of the mechanisms for vitamin B_{12} deficiency, leading to megaloblastic anemia, are the result of surgically produced abnormalities of the gastrointestinal tract. The basic mechanism is different for each lesion.

Total gastrectomy results in complete lack of intrinsic factor which is necessary for vitamin B_{12} absorption. It is believed that if patients survive long enough and are not given prophylactic vitamin B_{12} therapy, all would develop megaloblastic anemia.

Intestinal anastomosis leading to stasis of intestinal contents, with overgrowth of bacteria may cause vitamin B_{12} deficiency through bacterial interference with the utilization of vitamin B_{12}.

Use of radioactive vitamin B_{12} (cobalt^{60}-labeled B_{12}) has led to a better understanding of the pathogenesis of both types of megaloblastic anemia. The radioactive vitamin provides a useful tool for study of its absorption from the gastrointestinal tract.

THE OBSERVATIONS of Minot[14] in 1926 that hematologic improvement occurred in patients with pernicious anemia who were fed large amounts of liver started a series of investigations to determine the mechanisms involved in this fundamental clinical discovery. As a result of extensive clinical and biochemical studies over the succeeding 25 years it has been established that hematopoiesis is concerned with nucleoprotein metabolism, and that the vitamins, folic acid, ascorbic acid and vitamin B_{12} are all involved in very complex interrelationships concerned with nucleic acid chemistry.

Megaloblastic anemia may occur as a result of several fundamentally different mechanisms whereby a deficiency of either folic acid or vitamin B_{12} is brought about. Two of these mechanisms, both of which are incident to surgical operations on the gastrointestinal tract, will be dealt with in this presentation. Megaloblastic anemia may result from total removal of the stomach, and it may also occur after operations on the intestine where a blind loop of bowel is produced in association with intestinal anastomosis. When megaloblastic anemia occurs after either of these two surgical procedures, it is usually the result primarily of a deficiency of vitamin B_{12} rather than of folic acid. In most of the reported cases, pronounced reticulocyte responses occurred upon treatment with vitamin B_{12} parenterally. However, the mechanism whereby vitamin B_{12} deficiency occurs is a basically different one for each of the two surgically produced abnormalities. Although megaloblastic anemia resulting from total gastrectomy, or from the formation of an intestinal blind loop, is a rare occurrence, special studies with a few cases have thrown new light on the pathogenesis of the anemia in each instance and have contributed somewhat to understanding of hematopoiesis in general.

A valuable tool became available with the report of Heinle and co-workers[9] that cobalt^{60}-labeled vitamin B_{12} could be used to trace the absorption of this vitamin from the intestinal tract. Using a method whereby fecal excretion is measured after oral administration of 0.5 microgram of radioactive vitamin B_{12}, the author studied its absorption in 12 patients who had had a total gastrectomy and in three patients who had megaloblastic anemia associated with intestinal anastomosis and blind loop formation.

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MEGALOBLASTIC ANEMIA FOLLOWING TOTAL GASTRECTOMY

Castle's[4] experiments 25 years ago led to the concept that pernicious anemia is caused by deficiency of a gastric or "intrinsic" factor. Normally this reacts with a food or "extrinsic factor," and this reaction is necessary for normal erythrocyte formation. The extrinsic factor is now known to be vitamin B_{12}. The nature of intrinsic factor is not yet known precisely, although extracts of hog stomach mucosa[18] have now been fractionated and concentrated to such an extent that as little as 2 mg. mixed with vitamin B_{12} will result in a hematopoietic re-

TABLE 1.—*Absorption, in persons used as controls, of 0.5 microgram of orally administered cobalt^{60}-labeled vitamin B_{12}, as measured by subtracting fecal excretion from the oral dose.*

Case No.	Age	Diagnosis	Absorption Per Cent
1	37	No disease	59
2	64	Arteriosclerosis	74
3	31	No disease	80
4	48	No disease	70
5	48	Hypogonadism	71
6	32	No disease	67
7	45	Obesity	55
8	51	Dystrophia myotonia	67
9	30	No disease	68
10	34	Reiter's syndrome	81
11	24	Rheumatoid arthritis	43
		Average absorption = 68 per cent	

sponse when given orally to a patient with pernicious anemia in relapse. The exact mechanism whereby intrinsic factor exerts its effect is not known with certainty, but all the evidence indicates that it is necessary to enable vitamin B_{12} to be absorbed across the intestinal membrane.

Since 1929 a controversy has existed as to the site of origin of the intrinsic factor in man. It is known that in swine it occurs in the duodenum as well as the stomach, and for this reason it has long been thought by many hematologists to be present there in man, perhaps being secreted by Brunner's glands. This belief was strengthened by the fact that pernicious anemia does not develop in many patients who have had total gastrectomy, although it might be expected to develop in every case of total extirpation if the intrinsic factor were secreted nowhere but in the stomach.

Recent experiments[9] with radioactive vitamin B_{12} have shown that patients with pernicious anemia do not absorb it. Essentially the entire test dose can be recovered in the stools. However, when it is administered with normal human gastric juice, absorption becomes perfectly normal. The author also has noted these phenomena (Chart 1).

Absorption of vitamin B_{12} in a normal person is very limited. No matter how large a dose is given not much more than 1.5 micrograms can be absorbed.[18] In studies by the author it was observed that with a test dose of 0.5 microgram of cobalt^{60}-B_{12} the average amount absorbed in 11 persons was 68 per cent, the greatest absorption being 81 per cent and the lowest 43 per cent (Table 1). Almost identical data were reported by Callender, Turnbull and Wakisaka.[1] The reason for this extreme limitation of absorption of vitamin B_{12} is not yet known.

In studies of 12 patients who had had total gastrectomy[7, 19] it was noted that they had absorption of radioactive vitamin B_{12} almost identical with the absorption of patients with pernicious anemia. In every instance essentially the entire test dose of 0.5 microgram could be recovered in the stools. When normal human gastric juice was given with it, normal absorption occurred (Chart 2). Similar observations were made by Callender and co-workers[2] and by Ley.[10] Thus it appears that the site of origin of intrinsic factor in man is limited to the stomach. If it were produced in the duodenum or elsewhere in the gastrointestinal tract there should be some absorption of vitamin B_{12} as measured by the fecal excretion test with cobalt^{60}-B_{12}. Furthermore, megaloblastic anemia should not occur after total gastrectomy.

However, anemia that is indistinguishable from Addisonian pernicious anemia may develop. Combined system disease may occur as well as the other symptoms. The condition of the bone marrow and of peripheral blood are those of pernicious anemia. Since patients who have had total gastrectomy do not absorb any vitamin B_{12} from dietary sources,

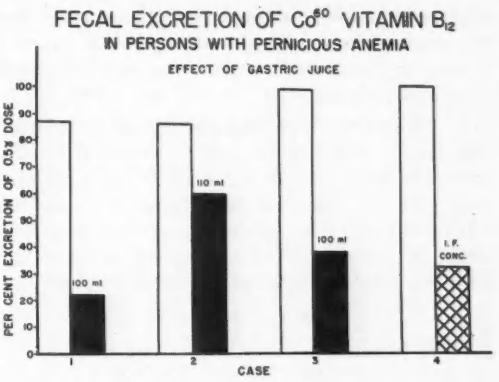

Chart 1.—Fecal excretion of cobalt^{60}-B_{12} in pernicious anemia (white columns), and the effect of normal human gastric juice (cases 1, 2 and 3), and of an intrinsic factor concentrate* (case 4), on excretion (black columns).

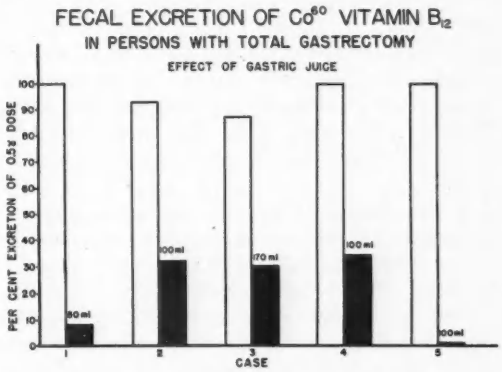

Chart 2.—Fecal excretion of cobalt^{60}-B_{12} in five patients who have had a total gastrectomy (white columns), and the effect of normal human gastric juice on excretion (black columns). Seven additional patients with total gastrectomy, similarly studied, showed identical patterns of excretion.

*Supplied by Dr. R. W. Heinle, Upjohn Company.

the question arises why megaloblastic anemia does not always follow total gastrectomy. There are four factors in the overall situation which adequately explain this paradox:

1. *Survival after the operation.* Total gastrectomy has been in wide use for only about ten years. The operative mortality rate is around 10 or 15 per cent, and survival longer than three years after operation for carcinoma (the indication in most cases) is about 20 per cent. Thus not many patients survive long enough for megaloblastic anemia to develop.

2. *Interval before development of anemia.* It may be that stores of vitamin B_{12} in the liver are sufficient for the patient's needs for several years. The daily human requirement of the vitamin is not more than 1.0 microgram. Assay of liver slices taken at autopsy showed that the human liver contains, on the average, about 1.2 milligrams of B_{12}[20]—enough to last almost four years. In pernicious anemia when therapy is stopped it has been shown that relapse may not occur for as long as three years.[15] Analysis of 46 cases of total gastrectomy by MacDonald and co-workers[13] revealed that megaloblastic anemia developed in 12. The anemia appeared four years or more after operation in nine of these cases.

3. *Completeness of gastrectomy.* Sometimes it is technically difficult to transect the cardiac end of the stomach above the cardioesophageal junction. Sometimes 1 to 2 cm. of cardia may be left in situ, yet the case be reported as one of total gastrectomy. Since in man the cardia is an active site of secretion of intrinsic factor a small amount left behind might provide an amount of intrinsic factor adequate for normal utilization of vitamin B_{12} contained in the diet.

4. *Prophylactic therapy.* It has been observed that even if prophylactic injections of liver extract or vitamin B_{12} are not advised by the surgeon, patients almost always receive multivitamin capsules. Many of these preparations contain folic acid, which would prevent megaloblastic anemia for some time. Many preparations now contain B_{12} and intrinsic factor concentrates. Only one of the 12 patients studied by the author had megaloblastic anemia but nine had received prophylactic therapy.

The patient with anemia was a 59-year-old man who had total gastrectomy in 1949 for carcinoma. Except for weight loss of 40 pounds which he could not regain he remained entirely well until September 1953, when he began to feel weak. Weakness progressed until the patient was admitted to the hospital in May 1954 with pronounced anemia. The hemoglobin content was 5.5 gm. per 100 cc. and erythrocytes numbered 1.39 million per cu. mm. There were no neurological abnormalities. The bone marrow

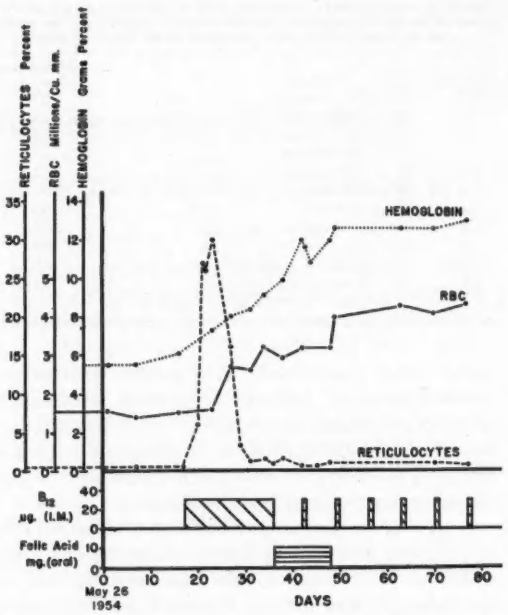

Chart 3.—Patient with severe megaloblastic anemia occurring four and a half years after total gastrectomy for carcinoma. Effect of vitamin B_{12} therapy on reticulocytes, hemoglobin, and erythrocytes.

was megaloblastic. The mean corpuscular volume was 109 cu. microns, mean corpuscular hemoglobin 35 micromicrograms per cell, and mean corpuscular hemoglobin concentration 32 per cent. A reticulocyte response of 30 per cent occurred on the sixth day of B_{12} therapy. Folic acid given later produced no additional response (Chart 3). Fecal excretion of cobalt^{60}-B_{12} was 95 per cent, but only 49 per cent was excreted when an intrinsic factor concentrate was administered with the test dose of radioactive vitamin B_{12}.

Considering the small number of patients who survive total gastrectomy long enough for megaloblastic anemia to develop, and considering the widespread use of antianemic medications, the rarity of megaloblastic anemia after the operation is not surprising. The evidence indicates, however, that every patient who does survive long enough and who does not receive prophylactic therapy will develop megaloblastic anemia indistinguishable from Addisonian pernicious anemia. An injection of 30 micrograms of vitamin B_{12} once a month would be adequate to prevent anemia indefinitely, and may be recommended as sound practice.

MEGALOBLASTIC ANEMIA ASSOCIATED WITH INTESTINAL ANASTOMOSES

In 1895 Faber[5] reported the case of a young woman in whom pernicious anemia was associated

with intestinal stricture. In 1929, Little, Zerfas and Trusler[12] found the characteristic clinical picture of pernicious anemia in a young man who had had several operations to cure an intestinal fistula following acute appendicitis. The operations resulted in anastomosis between jejunum and ascending colon, forming a blind loop of intestine and causing stasis of intestinal contents. Up to the present, reports of 79 cases can be found in the literature,[8] in which megaloblastic anemia is associated either with an intestinal stricture or surgically produced anastomosis which leaves a blind loop of gut. The common denominator appears to be the presence of an anatomical abnormality which causes stasis and stagnation of intestinal contents.

The anemia brought about in such cases is indistinguishable from Addisonian pernicious anemia. Glossitis, icterus and combined system disease have all been observed in this syndrome. However, both hydrochloric acid and intrinsic factor have been demonstrated repeatedly in the gastric juice. Thus the mechanism for the development of the anemia is not a lack of intrinsic factor as in pernicious anemia or the megaloblastic anemia of total gastrectomy. In many of the reports of recent cases it was noted that the patient responded to parenteral therapy with vitamin B_{12}. Surgical correction of the lesion that causes intestinal stasis may result in permanent cure of the anemia.

What the mechanisms are that bring about the anemia in such circumstances has been conjectural until recent years. One theory is that intestinal absorption is defective, as in sprue. However, steatorrhea is uncommon, and studies have demonstrated good absorption of fat and glucose. Thus it does not seem likely that this is the correct explanation. Beginning with Faber's case a luxuriant growth of bacteria throughout the small bowel above the stricture, or in the stagnant areas, has been noted often at autopsy. Faber suggested that the anemia was caused by absorption of a poison from the stagnant bowel contents. The anemia has been experimentally produced in dogs by bringing about intestinal strictures[16] and in rats after the construction of retroperistaltic blind pouches of small intestine.[3, 21] These observations indicate that intestinal bacteria have adverse effect on hematopoiesis.

With the advent of antibiotics it has been possible to investigate certain relationships between bacteria and hematopoiesis. Thus Lichtman and co-workers[11] obtained definite although suboptimal hematologic responses in pernicious anemia from aureomycin administration. In East Africa certain kinds of megaloblastic anemia were found to respond dramatically to oral administration of penicillin alone.[6] Finally two patients with megaloblastic anemia associated with intestinal anastomoses, studied in Finland, were treated with aureomycin and terramycin, and pronounced reticulocyte responses occurred.[17]

The author has observed three patients during the past year with megaloblastic anemia associated with intestinal stasis. Each had complete hematologic response to parenteral vitamin B_{12} therapy. Summaries of these cases follow:

CASE 1. A 19-year-old boy was admitted to Harbor General Hospital* with characteristic signs and symptoms of combined system disease and mild megaloblastic anemia. The anemia and all the neurological signs disappeared upon administration of vitamin B_{12}. At the age of ten the patient had had appendectomy followed by intestinal obstruction. He then had intermittent abdominal cramps until intestinal resection was performed at the age of 15. The exact nature of the anastomosis could not be ascertained. Following this the patient was entirely symptom-free until the anemia, with neurological disturbance, developed.

CASE 2. A 24-year-old Mexican man who worked in a hospital laboratory had several operations for intestinal obstruction and to correct internal fistulae which developed after appendicitis at the age of 13. The patient then was entirely well until ten years later, when weakness, pallor and soreness of the tongue developed. Studies revealed severe anemia and free hydrochloric acid in the gastric juice. Megaloblastosis was noted upon study of bone marrow aspirate. The patient was treated for six months with parenteral injection of B_{12} and symptoms were completely relieved. The injections were stopped and he remained well for 16 months. Then weakness and soreness of the tongue recurred. The patient was admitted to Wadsworth Veterans Administration Hospital in January 1954. Upon examination at that time, pallor and mild icterus were noted. Results of a neurological examination were within normal limits. The icterus index was 23 units at the time of admittance. Later it declined to 9 units. The result of an oral glucose tolerance test was normal. The hemoglobin content of the blood was 6.4 gm. per 100 cc. Erythrocytes numbered 1.8 million per cu. mm. and the packed cell volume was 19.5 per cent. The mean corpuscular volume was 108 cu. microns, the mean corpuscular hemoglobin 35 micromicrons and the mean corpuscular hemoglobin concentration 30 per cent. A barium study of the small bowel revealed dilated loops of ileum with stagnation of barium in the pelvic portion of the ileum for 24 hours. The patient was treated with vitamin B_{12}. Reticulocyte response of 16 per cent occurred and complete recovery ensued. At last report the patient was entirely well and was receiving 30 micrograms of B_{12} intramuscularly once a month.

CASE 3. A 60-year-old man had extensive diverticulosis of the entire small intestine. In 1949 a jejunal diverticulum perforated and a volvulus of

*Dr. Nancy Landon at Harbor General Hospital made possible the studies on this patient.

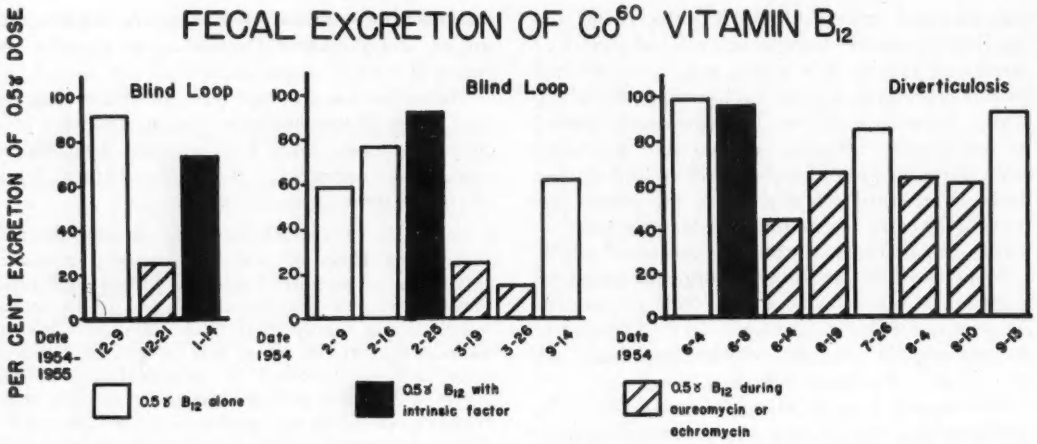

Chart 4.—Fecal excretion of cobalt^{60}-B_{12} in three patients with intestinal stasis. Two had blind loops, and one had diverticulosis of the small intestine. Note that excretion was very high. Intrinsic factor had no effect, but antibiotic administration resulted in significant decrease in excretion in all three.

the terminal ileum and cecum occurred. A resection of two feet of ileum with the cecum was performed, with end-to-side anastomosis of ileum to hepatic flexure. This resulted in a blind pouch of ascending colon.

In January 1952 the patient entered the hospital and was found to have mild macrocytic anemia. Upon examination of material from the bone marrow, megaloblastosis was noted. The hemoglobin content was 8.0 gm. per 100 cc. of blood, erythrocytes numbered 2.49 million per cu. mm. and the hematocrit 27 per cent. The mean corpuscular volume was 108 cu. microns, the mean corpuscular hemoglobin 32 micromicrons and the mean corpuscular hemoglobin concentration 30 per cent. Reticulocytes made up 0.4 per cent of total cells. There was free hydrochloric acid in the gastric contents. The stool did not contain an abnormal amount of fat. Treatment with vitamin B_{12} parenterally resulted in hematologic response, with reticulocytes increasing to 6 per cent of total cells. Folic acid was given to the patient later without further response.

Upon discharge the patient ceased taking vitamin B_{12} but continued to take folic acid orally. In May 1954 he was readmitted with recurrent diarrhea, pallor, weakness and weight loss of 25 pounds. Erythrocytes numbered 3 million per cu. mm. of blood, the hemoglobin content was 12.0 gm. per 100 cc. and the hematocrit was 33 per cent. Mean corpuscular volume was 110 cu. microns, mean corpuscular hemoglobin 40 micromicrons and mean corpuscular hemoglobin concentration 36 per cent. The result of an oral glucose tolerance test was normal. Vitamin B_{12} was given, 30 micrograms daily, and the reticulocytes rose to 4.8 per cent with a slow rise in hemoglobin, erythrocytes and hematocrit. Upon administration of aureomycin, diarrhea abated.

The foregoing clinical observations relative to the relationship of bacteria to hematopoiesis justify a hypothesis that an abnormal bacterial flora in the stagnant area of intestine may interfere with the utilization of vitamin B_{12}, resulting in B_{12} deficiency and megaloblastic anemia. In order to test this hypothesis the fecal excretion method for determining the absorption of radioactive vitamin B_{12} was used in the three patients with intestinal anastomosis. After the amount of cobalt^{60}-B_{12} excreted in the stools was measured, the patients were given either aureomycin or achromycin and the tests repeated. Two tests were done during the period of antibiotic administration in Cases 2 and 3, and one test in Case 1.

The results show that each patient excreted most of the test dose. However, they differed from patients with pernicious anemia in that intrinsic factor had no effect on absorption. During the administration of the antibiotic there was a pronounced decrease in fecal excretion in each case (Chart 4). The decreased excretion (or *increased absorption*) was much greater than variations found to occur spontaneously when tests were repeated in the same patient under the same conditions. In 14 patients in whom repeated tests were carried out the greatest variation was 18 per cent.

DISCUSSION

An explanation for the increased absorption of vitamin B_{12} and for the hematologic response which may occur in megaloblastic anemia during aureomycin administration is that bacterial competition for vitamin B_{12} is decreased. The impaired absorption of radioactive vitamin B_{12} might be explained by bacteria absorbing B_{12}, and thus denying it to the body. In these circumstances the radioactivity

recovered would be largely contained in the bacteria passed out in the feces. Certain strains of E. coli have pronounced avidity for B_{12} even though it may not be a growth requirement for these strains.

Although this is a plausible explanation, others do exist and it is quite likely that the mechanism is more complex than simple bacterial competition. Further study will be required in order to clarify the matter.

An interesting similarity comes to mind between the megaloblastic anemia associated with intestinal stasis and that occurring with fish tapeworm (diphyllobothrium latum) infestation in Finland. In both diseases the clinical picture is identical with that of Addisonian pernicious anemia, yet free hydrochloric acid and intrinsic factor secretion are normal. The fish tapeworm anemia can be cured by getting rid of the worm, just as the megaloblastic anemia of intestinal stagnation can be cured by surgical correction of the underlying lesion or, apparently, by changing the bacterial flora with antibiotics. Finally, although the underlying factors causing the anemia (intestinal blind loop on the one hand, intestinal parasite on the other) are extremely common, vitamin B_{12} deficiency, leading to anemia, does not occur very often.

In the management of a patient with anemia caused by intestinal lesions it would seem logical to correct the anatomical abnormality surgically, but only if this appears to be technically simple. An injection of 30 micrograms of vitamin B_{12} once a month will control the deficiency which causes the anemia. In none of the three cases herein reported was it felt that operative correction of the intestinal abnormality was indicated.

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Chlorpromazine Alone and with Reserpine

Use in the Treatment of Mental Diseases

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• *One hundred psychiatric patients were treated with chlorpromazine, alone or combined with reserpine. Fifty-six per cent of patients with chronic schizophrenic reactions showed moderate or pronounced improvement when treated with chlorpromazine alone. The results of treatment with the combined drugs were not so good as that. Indications are that treatment of patients with chronic schizophrenic reactions is more efficacious with these drugs than with other forms of somatic therapy.*

Complications of treatment were far greater with combined use of chlorpromazine and reserpine. For this reason, the combination appears to have limited usefulness. The Parkinson syndrome was the most frequent complication of large doses of these drugs. It appears to be a toxic reaction, requiring reduction in dosage. Jaundice appears to be neither a frequent nor a serious complication of treatment.

TWO DRUGS of great promise in psychiatry recently appeared almost simultaneously. Chlorpromazine, a synthetic drug of the phenothiazine group, was initially introduced as a potentiating agent for anesthetic agents. Reserpine, a pure alkaloid of Rauwolfia serpentina, was produced primarily as a treatment for hypertension. Both drugs, although of different origin and chemical structures, have similar effects on the nervous system and on patients with mental disorders.

In the short span of its use in psychiatry, numerous favorable reports have appeared on the use of chlorpromazine.[3, 7, 10] Little has been written about the combined use of reserpine and chlorpromazine. This study is an assessment of the usefulness of chlorpromazine, alone and combined with reserpine, in psychiatric treatment.

METHOD OF STUDY

Chlorpromazine was used alone in 68 psychiatric patients and in combination with reserpine in 32 patients. The psychiatric diagnoses of patients treated with the single drug were chronic schizophrenic reaction in 50, personality disorder in three, psychotic depressive reaction in one, and various organic psychoses in 14. All the patients treated with the combined drugs had chronic schizophrenic reactions.

The 82 patients with chronic schizophrenic reactions ranged in age from 18 to 77 years; the median age was 34 years. Duration of illness varied between six months and 35 years. Forty-three of these patients had been ill for nine years or more. Sixty-six patients had received some somatic therapy before. Twelve had been treated with bilateral prefrontal leukotomy. The 14 patients with organic psychosis ranged in age from 57 to 80 years. Ten patients had chronic brain syndromes due to senile or arteriosclerotic brain disease, two were syphilitic, one was epileptic and one suffered from the effects of trauma.

Initial trials of treatment utilized the double-blind technique. In all patients except those with organic psychoses, treatment was initiated on a medical treatment ward. Forty patients, most of them schizophrenic, were treated with chlorpromazine or placebos. The dose used was 150 mg. intramuscularly for three to four days followed by oral doses of 100 to 400 mg. daily. Twenty-six patients, all schizophrenic, were treated with a combination of chlorpromazine and reserpine or identical placebos. Two dosage schedules were used: (1) Seven days of parenteral therapy with 50 mg. of chlorpromazine and 5 mg. of reserpine daily followed by oral doses of 200 mg. of chlorpromazine and 3 mg. of reserpine daily; (2) seven days of parenteral therapy with 100 mg. of chlorpromazine and 2.5 mg. of reserpine daily followed by oral doses of 300 mg. of chlorpromazine and 2 mg. of reserpine daily.

After treatment was under way, patients were returned to their usual wards. A preliminary evaluation was made by each patient's psychiatrist during the third week of the trial. Patients who had received active medication were continued on treatment, a flexible dosage schedule being used. Patients who had received placebos were started on the same schedules of active medication. Twenty-eight patients with organic psychosis were treated

From the Veterans Administration Hospital, Palo Alto.

Chlorpromazine for these studies was supplied by Smith, Kline and French Laboratories; Reserpine by Ciba Pharmaceuticals, Inc.

TABLE 1.—*Results of double-blind studies on 66 patients with schizophrenic reactions treated with Chlorpromazine and combinations of Chlorpromazine and Reserpine*

Treated with	Improved	Unimproved	Worse	Total
Chlorpromazine	13	11	0	24
Placebo	3	15	0	18
Chlorpromazine-reserpine combination	9	6	2	17
Placebo	1	6	0	7

with a daily dose of 75 mg. orally of chlorpromazine or identical placebos. At the end of 40 days of treatment, an evaluation was made.

Longer term evaluations were made of patients after they had been on treatment with chlorpromazine alone for two to eight months. Most of these patients were started on parenteral doses of chlorpromazine followed by oral maintenance doses of 100 to 800 mg. daily. Only seven patients in this series received a daily dose of more than 500 mg. of the drug. In the case of patients receiving the combined drugs, an evaluation was made at the end of three to four months of treatment. Seventeen patients received the dosage schedule using higher doses of reserpine, while 15 patients received one using higher doses of chlorpromazine. Fifteen patients were not maintained on the combination for the entire course, but were switched to maintenance doses of one drug or the other. In all cases, the reason for this change was the development of some complication of treatment.

All evaluations were made by the psychiatrist familiar with the patient prior to treatment. In general, patients were considered to have shown slight improvement if they were appreciably less disturbed, required less sedation, seclusion or restraint, or could be moved to a ward with less severely ill patients. Criteria for the classification *moderate improvement* were: (a) No further requirement of seclusion or restraint and a markedly diminished need for other forms of sedation, (b) improvement in behavior which permitted the patient to participate in activities programs or group and individual psychotherapy, and (c) social improvement which made possible the granting of ground privileges or passes from the hospital for the first time. *Marked improvement* implied that the patient had made a great change according to the criteria listed above and that he was being considered for release from the hospital. The patients with organic psychosis were evaluated only in terms of whether the drug was satisfactory in controlling aberrant behavior.

RESULTS

The results of the double-blind studies in patients with chronic schizophrenic reactions are summarized in Table 1. The number of patients who improved on active medication was convincingly greater than the number who improved on placebos. Judging solely by the proportion of patients who improved in each group, it might be concluded that the combined drugs were at least as effective as chlorpromazine alone. However, the degree of improvement was frequently greater in the patients who received chlorpromazine alone. Two patients became temporarily worse when the combined drugs were used. A few other patients were so profoundly affected when the combination was used that it became obvious that they had received active medication rather than placebos. However, the evaluations made on these patients were as objective as possible.

TABLE 2.—*Results of treatment of 82 patients with schizophrenic reactions with Chlorpromazine and combinations of Chlorpromazine and Reserpine*

	Chlorpromazine Alone	Chlorpromazine-Reserpine Combination	Total
Unimproved	8	6	14
Slightly improved	14	16	30
Moderately improved	19	8	27
Markedly improved	9	2	11
Total	50	32	82
Total with moderate or marked improvement	28 (56%)	10 (31%)	

The results of longer treatment of patients with chronic schizophrenic reactions are summarized in Table 2. Fifty-six per cent of patients treated with chlorpromazine alone showed moderate or pronounced improvement. Only 31 per cent of patients treated with the combined drugs showed similar degrees of improvement. Although patients treated with the combined drugs were not treated for as long a period, the dose of drug they received, on the basis of expected additive effect, was greater.

Thirteen of the 82 schizophrenic patients were allowed to leave the hospital for the first time on trial visits or leaves of absence. Others approached this degree of improvement. Only one of the 82 patients required treatment with electroconvulsive therapy along with the drug. Five of the 12 patients who had not responded to bilateral prefrontal leukotomy were moderately or considerably improved by the drugs.

Those schizophrenic patients who showed moderate or pronounced improvement were usually better than they had been at any time since their illness began. Often the change in patients was dramatic, both in the rapidity of onset and in the degree. However, in some patients improvement took a more gradual course. Delusions and hallucinations diminished considerably. Mute and apathetic patients often began to speak appropriately.

TABLE 3.—*Complications of treatment of 100 psychiatric patients with Chlorpromazine and combinations of Chlorpromazine and Reserpine*

Complications	Chlorpromazine Alone 68 Patients	Chlorpromazine-Reserpine Combinations 32 Patients
Parkinson syndrome	4	9
Excitements	0	7
Convulsions	3*	3
Jaundice	2	1
Reactivation of peptic ulcer	2	0
Skin eruption	0	1
Syncope	1	0

*One patient had previous seizures.

Severely disorganized speech gradually became more coherent. A few patients seemed to have amnesia for their illness, expressing astonishment upon hearing how long they had been hospitalized. The changes in physical appearance were also noteworthy. Nutrition was improved, dress became neater, and social amenities were restored. Most of these patients, who had previously spurned any psychiatric treatment, appeared now to be able to participate fruitfully in it.

The results of treatment of patients with organic psychosis using a daily dose of 75 mg. of chlorpromazine orally were not striking. Six of 15 patients who received active medication improved. However, three of 13 patients who received placebos improved. It was decided that a higher dose of the drug would be needed to treat patients in this group effectively. Seven of 14 patients who were then treated with a daily dose of 150 to 200 mg. of chlorpromazine showed satisfactory improvement. In general, the degree of disability shown by these patients was not greatly changed by this dose of the drug. In these older patients, higher doses of the drug were sometimes not well tolerated.

The results of treatment were disappointing in three patients with personality disorders and one patient with a psychotic depressive reaction. None of these patients was helped. Two of the patients with personality disorders became depressed from the drug. The patient with a psychotic depressive reaction was made worse, having more disturbing hallucinations.

Complications of treatment occurred with considerably greater frequency in patients who received combined treatment than in those who received chlorpromazine alone (Table 3). The frequent appearance of the Parkinson syndrome, excited states and convulsions is noteworthy in this group. Often two of these complications occurred simultaneously in the same patient, suggesting that all of them were related to the same toxic effect on the central nervous system. Among patients treated with chlorpromazine alone, these toxic effects occurred only when daily doses of 400 mg. or more of the drug were used. All of these side-effects were completely reversible by temporary interruption of treatment or by reduction in dosage.

The appearance of jaundice was not related to the dose of drug used. This complication occurred within nine to twenty-four days after treatment was begun. Two patients had prodromal symptoms of fever, gastrointestinal disturbances and malaise. Characteristic laboratory abnormalities were elevation of serum bilirubin, alkaline phosphatase, cholesterol and phospholipids. Only one patient had a laboratory sign of parenchymatous jaundice. In his case the result of a cephalin flocculation test was positive. Biopsy of the liver in this patient gave evidence of bile stasis and cellular infiltration around the biliary radicles. The longest duration of jaundice was three weeks, while in one patient jaundice disappeared in 48 hours. This latter patient had had viral hepatitis four years earlier and at that time jaundice had lasted for several weeks. (One patient, not in this series, has been successfully maintained on treatment with chlorpromazine after two brief episodes of jaundice.)

Other complications of treatment were infrequent. Skin eruptions occurred with less frequency than was anticipated. On the other hand, one patient with numerous infected lesions from compulsive scratching became completely free of lesions after treatment. Another patient with psoriasis was improved. Two patients with reactivation of peptic ulcers were continued on treatment by the addition of an ulcer regimen. Two patients died while under treatment, but in neither instance could the death be related to the drug. One patient drowned; the other had a ruptured abdominal aneurysm.

COMMENT

The effectiveness of chlorpromazine in psychiatric treatment cannot be doubted. Especially encouraging is the frequent amelioration of psychotic symptoms in patients with chronic schizophrenic reactions. In the present series 56 per cent of such patients were moderately or greatly improved by this drug. In a series reported elsewhere, 54 per cent of such patients treated with reserpine in combined parenteral and oral doses showed similar degrees of improvement.[4] Thus, in the authors' experience, both drugs have been equally effective in this most difficult group of patients. It should be emphasized that it is the practice of the authors to continue other forms of treatment while the patients are treated with drugs. Thus, these results represent more than the effects of the drugs alone.

The combination of chlorpromazine with reserpine does not seem to offer any advantage over the

use of either drug alone. At lower levels of dosage, no advantage from the use of combined drugs as opposed to use of reserpine alone[5] was noted. In larger doses, use of combined drugs enhanced the toxic effects, particularly those affecting the central nervous system. Quite possibly there exists a middle range of dosage where the combination can be used effectively.[1] However, whether the combination is superior to equivalent doses of either drug alone is questionable.

There seems to be little indication for the use of chlorpromazine in patients with personality disorders or psychotic depressive reactions. In the latter patients, the authors agree with other investigators[6] that electroconvulsive therapy is the treatment of choice. While behavioral aberrations can be controlled in some patients with organic psychosis, there is little reason to believe that this drug can rehabilitate patients with advanced degrees of organic change.

Since the wide use of reserpine and chlorpromazine was begun at the Veterans Administration Hospital, Palo Alto, no patient has been subjected to leukotomy. The use of electroconvulsive therapy in the treatment of schizophrenic patients has diminished to the vanishing point. There is every reason to believe that the drugs are better than either of the other somatic therapies. The fact that almost half of a group of patients in whom leukotomy did not help obtained significant improvement from drug treatment tends to confirm this conclusion. On the other hand, more effective use of psychotherapy for schizophrenic patients now seems to be possible.

The importance of jaundice as a complication of chlorpromazine therapy seems to have been exaggerated. The incidence of 3 per cent in this series is higher than the over-all incidence of 0.9 per cent reported in 3,533 psychiatric patients who were treated with the drug.[9] In any case, the risk does not seem to be greater than the experience here reported would indicate. Furthermore, the jaundice is of mild degree and short duration. It resembles most of the jaundice produced by methyltestosterone.[8] As yet, there is no reason to believe that permanent hepatic damage ensues from this complication.

The production of the Parkinson syndrome by either chlorpromazine or reserpine, and particularly by the combined drugs, is a matter not to be treated lightly. All the evidence to date indicates that this syndrome represents a toxic effect of these drugs.[2] With the usual remedy for toxic effects, diminution of dosage, this phenomenon disappears. To continue treatment in the face of this syndrome may be courting disaster. There is a point at which physiologic effects may become pathologic changes. Until more is known about the implications of this complication, the utmost of prudence is indicated.

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Introduction to Muscle Relaxants

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• The first writings of curare appeared about 1500. Two hundred and fifty years later the first real experimentation took place with the drug and an additional two hundred years elapsed before the drug found its true place in medicine. During the past decade it has become a valuable drug in anesthesia.

The muscle relaxants have been divided into two groups according to their action — the curare-like or competitive inhibition blocking group, and the C-10-like or depolarizing blocking group. They act at the myoneural junction to produce relaxation with very little effect on the remainder of the body. In recent years the synthetic curare-like drugs have overshadowed purified curare.

ALTHOUGH TODAY many drugs can be classified as muscle relaxants, it was but a short time ago that curare was the only agent generally thought of in this regard—and only a relatively few years have passed since even curare was, to most persons, only a deadly poison used by South American Indians on the tips of arrows. *Curare* is an English word,[10] and attempts to trace its origin become quite confusing. Some investigators think that the original word was *uirery*—taken from *uira*, meaning *bird*, and *eor*, meaning *to kill*. Others believe it comes from *urari*—taken from *ur*, meaning *to come*, and *ar*, meaning *to fall*. Still others feel it comes from Curwara[3]—the name of a river in Guiana. Many referred to the drug as "wouralia."

The first writings of curare, at about the beginning of the Sixteenth Century, were by D'Anghera,[10] an Italian living in Spain who got his information from sailors returning from the Americas on the original Columbus expedition. Certain conclusions can be drawn from these early writings. First, several types of arrow poisons were known. The leaves,[14] stems, roots and bark of many plants were used to make water extracts and hence there was great variety in potency. For many years three main types[10] were known—tubocurare, calabash curare and pot curare—the designation depending on the type of containers in which the preparations were stored; that is, bamboo tubes, gourds or earthenware pots. The drugs[14] themselves might or might not be the same; the distinction was not between drugs but between containers. This, of course, led to many discrepancies in experimental work throughout the years.

Through D'Anghera's[10] writings one finds also that cauterization of wounds that were caused by arrows dipped in curare was practiced by the natives, and it was thought that some of the tribes had an antidote. Some of the early so-called antidotes were tobacco, salt, salt water, urine and sugar. All of them and others besides were put immediately into the wound in the hope of preventing death.

Many weird tales[10] arose about the ingredients of this poison. Some of the ingredients were thought to be teeth and livers from venomous snakes, red peppers and stinging ants. Because of the suspicious nature of the natives, it was not until about 1839 that a foreigner, Richard Schomburgk, was allowed to witness the preparation of the deadly arrow poison. It was his opinion that *Strychnos toxifera* was the plant from which came the active ingredient.

Sir Walter Raleigh[10] is given credit for taking the first curare to Europe (in 1584) and presenting it to Queen Elizabeth. McIntyre, a pharmacologist, believes this to be false and blames Munter's misreading of Caley's "Life of Raleigh" for this misconception.

The first real experimentation with the drug was carried on in 1745 by De la Condimine.[3] Searching for an antidote, he used sugar and obtained, he thought, a certain degree of success.

Fontana[3] in 1781 made several important observations. Some of these were: (1) That vapors from the extraction process were not harmful; (2) that acids and alkalies were not antidotes; and (3) that voluntary muscle irritability is destroyed.

In 1811 Brodi and Bancroft[3] were first to observe the effects on respiration and first to support life in a curarized subject with artificial respiration in the form of a bellows connected to a cannulated trachea.

In 1821 Humboldt[10] reported the subjective symptoms in Indians who recovered from poisoning. These symptoms were "congestion of the head," vertigo, nausea and vomiting, extreme thirst, and numbness about the wound.

About 1814 Waterton[10] gave an ass wourali in the shoulder and after the animal apparently died,

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revived it with artificial respiration by attaching a bellows to the windpipe. After four hours the animal finally took over respiration on her own and survived the ordeal although she was "lean and sickly for about a year." She was given the name "Wouralia" and sent from London to a farm in the country. According to Waterton: "Wouralia shall be sheltered from the wintry storm; and when summer comes, she shall feed in the finest pasture. No burden shall be placed upon her and she shall end her days in peace." With this care she survived nearly 25 years. This led to Sibson's work with the use of curare in the treatment of tetanus in horses—the first clinical use of the drug.

In 1844 Claude Bernard[8] turned his attentions to curare and muscle-nerve preparations. Some of his conclusions were that irritability of curarized muscle remained unimpaired and the nerve also retained its functional activity.

The first man to use curare in tetanus in a human was Sayers.[10] In 1858 he applied curare locally to a wound in the thumb. Results were poor and the patient died. In the years that followed, curare was used repeatedly for treatment of patients with tetanus, with various degrees of success.

Pal[2] in 1900 reported eserine curare antagonism.

West[3] in 1932 used curare in the treatment of spastic disorders—Parkinson's disease, parathyroid tetany, epilepsy and hemiplegia. His results were rather variable; the drug he was using was not standardized.

In 1939 Bennett[3] began using curare as a safety factor against fractures in metrazol shock treatment. His work was aided when, in the same year, a manufacturer of pharmaceuticals supplied him with a standardized form of curare—Intocostrin®—which is derived from the plant *Chondodendron tomentosum*.

Wright[3] persuaded Griffith and Johnson to use it in anesthesia and in 1942 they reported their first series of cases. Cullen soon followed with his series.

By 1943 Wintersteiner[14] and Dutcher found the active principle of Intocostrin in crystalline form and called it d-tubocurarine chloride.

In 1949 Barlow and Ing[7] through careful chemical planning synthesized decamethonium bromide (Syncurine®), a 10-carbon compound separating quarternary nitrogen atoms.

Succinylcholine[4] (Anectine®) was originally synthesized in about the year 1906 but its true actions were not appreciated and put to practical use until 1950 when the British first used it. In 1952 it was introduced into this country.

Since the introduction of the muscle relaxants into anesthesia, many drugs such as Beta-erythroidine, Myanesin,® Tolserol® and Mytolon chloride have come into use.

PHARMACOLOGY

In normal tissue[8] an impulse arrives at the end of the nerve fiber and acetylcholine is released into the subneural space, causing depolarization of the postjunctional membrane and contraction of the muscle. The acetylcholine is hydrolized by cholinesterase almost immediately and, following this, repolarization takes place and the muscle can again contract upon further impulse through the nerve.

Claude Bernard[8] set down several requirements of a neuromuscular blocking agent: Response of the muscle to stimulation through its motor nerve must be abolished, nerve tissue conduction must remain unimpaired and the muscle must be capable of responding to direct electrical stimulation. Recently it was added that acetylcholine release should continue during paralysis. These requirements are met by the drugs that are included in this discussion.

The neuromuscular blocking agents can be divided into two groups according to their action. The first group is the curare-like or competitive inhibition blocking group; the second is the C-10-like or depolarizing blocking group.

The curare-like group blocks by raising the threshold of the postjunctional membrane to acetylcholine.[8] This action can be reversed by the anticholinesterase drugs which permit acetylcholine to accumulate and destroy the blockade. The paralysis is flaccid, is antagonized by anticholinesterase drugs, and is potentiated by ether anesthesia.

The drugs included in this group with similar actions are d-tubocurarine, gallamine (Flaxedil), the dimethyl ether of d-tubocurarine (Metubine iodide and Mecostrin) and benzoquinonium chloride (Mytolon).

The C-10-like[8] drugs are represented by decamethonium. They produce relaxation by persistent end-plate depolarization. After relaxation is effected, contraction cannot come about again until repolarization takes place, and this cannot happen as long as decamethonium is present. Flaccid paralysis occurs and anticholinesterase brings about potentiation of blockade. Potency is unaffected by ether. Succinylcholine belongs with decamethonium in this group.

For many years it was thought that curare possessed a central depressive action and analgesic properties until Smith,[14] in 1947, reported proof that it neither stimulates nor depresses the central nervous system and does not bring about analgesia. He made these observations by remaining awake while being given enough curare to produce complete flaccid paralysis.

Landmesser[9] in 1947 commented that Intocostrin and d-tubocurarine chloride, curarine chloride and quinine methochloride produce bronchoconstriction and a drop in blood pressure through the liberation of histamine from the body tissues. Antihistamine given prophylactically helped to prevent the bronchoconstriction. He also observed dose-to-dose refractoriness with the above drugs.

With therapeutic doses[1] there is no significant effect noted on the temperature regulating center, vasomotor center, vomiting center and respiratory center and cough center.

The muscles of the lids and eyeballs are first to be involved,[14] then the facial muscles. The neck muscles are paralyzed next. The diaphragm is the last voluntary muscle to be paralyzed. Massive fasciculations[6] have been seen with the use of succinylcholine, caused by depolarization of the motor end plate membrane. This effect can usually be prevented by slower administration.

Metabolism and body temperature are reduced due to decreased muscular activity.[1] In the autonomic nervous system a depression of conduction in both sympathetic and parasympathetic ganglia has been noted.[14]

The uterus is not relaxed by therapeutic doses. Pittinger and Morris[12, 13] found that d-tubo, gallamine and succinylcholine crosses the placenta in dogs when injected in the uterine artery. Decamethonium did not cross the placenta with this technique.

Curare is partly detoxified in the liver. The remainder is eliminated unchanged by the kidney into the urine. Foldes and co-workers[5] reported that about 3 per cent of Succinyldicholine is excreted unchanged and that the remainder is broken up by cholinesterase, particularly "pseudo" cholinesterase of the plasma into succinylmonocholine and eventually succinic acid and choline. Cumulation or tachyphylaxis has not been observed with succinylcholine.[4]

In comparing the potency of the various muscle relaxants, if d-tubocurarine is considered as the standard, it is observed that gallamine is about one-fifth as potent, succinylcholine slightly more than one-third as potent, benzoquinonium about the same potency, dimethylether of d-tubocurarine about 4.7 times as potent and C-10 about 5.8 times as potent.[8]

In conclusion, a few statements about present-day antidotes: Neostigmine,[8] an anticholinesterase drug, allows a build-up of acetylcholine and the blockage by d-tubocurarine is destroyed. However, this is not as simple as it sounds and atropine must be given to counteract the bradycardia, intestinal colic and salivation produced by neostigmine. Overdosage of neostigmine may bring about pronounced vasodepression. Tensilon is thought to counteract the effects of curare by displacing the curare molecules at the postjunctional membrane. However, some investigators feel that its action is that of an anticholinesterase drug. The danger occasionally encountered is that the action of Tensilon may wear off and partial or complete curarization remain.

These procedures are ineffective against the C-10 group. Blood transfusions[11] have been used to increase the "pseudo" cholinesterase of the plasma with occasional success.

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Muscle Relaxants

Effects on Respiratory and Circulatory Dynamics

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• There are exceptions and variations to the general clinical rule that muscle relaxants depress respiration and have no effect on circulation.

Variation may be attributed to differences in animal species, in individual response, in muscle affected, in drug used and in dose employed.

Conclusions about muscle relaxants derived from animal experiments cannot always be assumed to apply to man.

The "respiratory sparing" action of a muscle relaxant cannot be relied upon in any individual patient. Facilities for adequate artificial respiration must always be available when any dose of any muscle relaxant drug is administered.

Muscle relaxants affect circulation by inhibition of parasympathetic and sympathetic ganglia, by anticholinesterase activity and by release of histamine.

MUSCLE RELAXANT DRUGS are administered primarily for the purpose of diminishing the activity of skeletal muscle. Rarely are they administered for their effects on respiration or circulation. Therefore, effects of these drugs on respiration and circulation are considered complications or side effects. The general rule is that muscle relaxants cause a depression of respiration and cause little or no effect on circulation. This rule is sufficiently constant to be useful clinically, but there are exceptions to it. Some of the exceptions and variations have clinical applications while others serve only to excite curiosity and to stimulate further investigation of this group of useful drugs.

To discuss the exceptions to the usual effects of muscle relaxants it is necessary to outline the circumstances under which the exceptional effects occur. Although the present discussion is primarily limited to the effects of muscle relaxants on respiratory and circulatory dynamics, it will include comparative effects of muscle relaxants on other systems. The effect of muscle relaxants may vary (1) with the species of animal to which it is administered, (2) with the individual differences in members of the same species, (3) with the type of muscle being observed in any given animal, (4) with the pharmacological group to which the single relaxant drug belongs and (5) with the dose administered and with the influence of concomitantly administered drugs.

Variation Due to Species

The neuromuscular junction where the muscle relaxants exert their principal effect is a basic physiological unit and it would be logical to expect it to function similarly in most animals. However, Paton and Zaimis[18] showed that in the cat decamethonium affects the tibialis anterior muscle more than the soleus muscle, while in the monkey the order is reversed and the same drug in small doses exerts a greater effect on the soleus muscle than on the tibialis muscle. In this respect the muscle of man acts more like that of the cat than that of the monkey. The muscles of respiration respond in a manner similar to that of the soleus muscle. Paton[16] also showed that species sensitivity to muscle relaxants such as d-tubocurarine with a competitive type of action increases as follows, man and cat, rabbit, mouse, rat. The sensitivity to muscle relaxants with a depolarizing type of action is just the reverse. In general there is less species variation response to d-tubocurarine than there is to decamethonium.

These differences of reactions among the species are difficult to explain. Foldes[10] offered the suggestion that the difference in action may be due to the difference in the proteins of the receptors for acetylcholine at the myoneural junction. Whatever the cause, the indication is clear that conclusions about muscle relaxants that are based on results of animal experiments cannot always be assumed to apply to man.

Variation Due to Individual Response

Even individuals of the same species do not always respond to muscle relaxants in the same manner. In man there is a definite individual variation

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in the degree of sensitivity to the muscle relaxants but there is no characteristic racial pattern. Age may influence response. Stead[19] observed that newborns require twice the adult dose of suxamethonium per kilogram of body weight to produce comparable effects. On the other hand, newborns are more sensitive than adults to d-tubocurarine and exhibit a response somewhat like the adult who has myasthenia gravis.

It is well known that patients with myasthenia gravis are very sensitive to muscle relaxants with a competitive type of action, and a small fraction of the average dose for normal individuals may lead to prolonged respiratory arrest. Churchill-Davidson and Richardson[5] emphasized the less well known fact that in patients with myasthenia the threshold for decamethonium is elevated. Decamethonium exerts a depolarizing type of action in normal patients, but in patients with myasthenia it has a competitive type of action as shown by the reversal of its effect by anticholinesterase and by the absence of muscle twitching.

It is characteristic of decamethonium and certainly of suxamethonium that the duration of inhibition of both skeletal and respiratory muscles is less than the duration of action of equivalent doses of d-tubocurarine and other muscle relaxants with a competitive type of action. For some as yet undetermined reason the inhibition of respiratory muscles by these two relaxants in certain patients may be prolonged and apnea of a duration up to nine hours has been reported following administration of suxamethonium. Dripps[8] reported unexpectedly prolonged respiratory depression in 13 patients out of 2,800 receiving muscle relaxants during surgical anesthesia, an incidence of 1 in 215. He classified into two groups the theories advanced to explain these rare instances of prolonged respiratory inhibition—theories of central action and theories of peripheral action. The reasons for believing that the prolonged apnea may be due to effects on the central nervous system are that in some patients with prolonged apnea the diaphragm can be made to contract by electrophrenic stimulation and some apneic patients make voluntary movements with skeletal muscles before they are able to breathe. This is the reverse order of normal muscle recovery since the respiratory muscles are usually the last to be paralyzed and the first to recover following administration of muscle relaxant drugs. However, Bovet and Longo[3] found no electroencephalographic evidence of central nervous system depression in rabbits that received up to 100 times the respiratory paralyzing dose of several muscle relaxants. Not only was there no change from the normal electroencephalographic pattern of these rabbits, but the expected electroencephalographic response to external stimuli and to the administration of barbiturates and several other drugs was not altered.

Reports on the incidence of prolonged recovery from medication with suxamethonium are variable: 1:1200,[1] 1:200[9] and 1:66.[2] The two patients of Evans and co-workers[9] who were apneic for 20 minutes after single doses of suxamethonium had plasma cholinesterase levels only 10 per cent of normal. From this experience they expressed their intention to use blood transfusion to treat any future prolonged respiratory depression following suxamethonium medication. Later Harrison and co-workers[13] reported success using a small fresh blood transfusion to treat a postsuxamethonium respiratory depression of five hours' duration which had not responded to other therapy. Such experiences have led to the acceptance of the warnings that (1) small test doses of suxamethonium should precede therapy with the drug, (2) equipment and experienced personnel for endotracheal intubation and adequate artificial respiration should be readily available when even small doses of suxamethonium are to be used and (3) the drug should be used with caution for patients with pathological conditions frequently associated with low plasma cholinesterase levels, such as severe liver disease, malnutrition, and exposure to insecticides or war gases.

There is some evidence that low plasma cholinesterase concentration is not the only cause of prolonged respiratory depression following administration of suxamethonium. Of the seven patients of Argent and co-workers[1] with prolonged respiratory depression, six had plasma cholinesterase levels greater than 50 per cent of the levels of controls. Bourne[2] measured the plasma cholinesterase of ten patients who showed delayed recovery of respiration following suxamethonium and found the level below normal in eight and at the lower limits of normal in two. The author has observed only two patients whose recovery of respiratory function was delayed following use of suxamethonium with surgical anesthesia—an incidence much less than any in the reports reviewed—and on the basis of this meager experience is inclined to agree with the statement of Goodman and Gilman:[11] "It represents the cumulative effect of overdosage and can almost invariably be avoided by properly regulating the rate of drug administration."

Variation Due to Muscle Type

Why some muscles are paralyzed to a greater degree by different muscle relaxant drugs than are other muscles has not been explained. According to our present expanding knowledge of neuromuscular physiology, the chemical and electrical changes seem to be similar in most voluntary muscles. Per-

haps the theory of Foldes[10] concerning the character of the proteins associated with neuromuscular junction receptors may as well explain muscle variation as species variation in their response to muscle relaxants.

According to Goodman and Gilman[11] d-tubocurarine causes respiratory paralysis in cats with minimal effect on the tibialis muscle while decamethonium causes only slight respiratory depression in a dose sufficient to paralyze completely the tibialis muscle in the same animal. The reaction of red, slowly acting postural and respiratory muscles seems to be different from that of white, quickly contracting muscles.

In man decamethonium has been thought to have a "respiratory sparing" action when compared to d-tubocurarine by clinical observation. The same has been claimed for the dimethyl ether of d-tubocurarine. When Unna and co-workers[20] measured the human respiratory vital capacity after hand grip strength had been decreased 95 per cent by various muscle relaxants, they found that decamethonium reduced the vital capacity 61 per cent, d-tubocurarine 31 per cent and dimethyl d-tubocurarine only 16 per cent. This substantiates the clinical impressions concerning dimethyl d-tubocurarine but opposes the clinical impressions about the "respiratory sparing" action of decamethonium in man.

Most anesthesiologists agree that in some patients adequate relaxation of the abdominal muscles can be achieved with only slight respiratory depression whereas in other patients it may be necessary to abolish almost all voluntary respiratory activity in order to achieve adequate abdominal muscle relaxation. Occasionally a surgeon finds abdominal relaxation inadequate even though the patient has been rendered completely apneic by a muscle relaxant. While it is probable that some such complaints are the result of surgical technical problems, in the author's experience these complaints have usually come near the end of a long surgical procedure when the only remaining problem is closure of the abdominal wall. In the light of the reports of the prolonged apnea following suxamethonium, even though the patient is able to control skeletal muscle, it is possible that the surgeon has been correct about his complaints more often than the anesthesiologist has been willing to agree.

It is hoped that in the future agents will be available for selective paralysis of single groups or types of muscles. Until then, it would seem to be in the interest of the patient's safety for the anesthesiologist to assume that any dose of any muscle relaxant sufficient to produce moderate relaxation of skeletal muscle will also bring about inadequate or marginal pulmonary ventilation. Therefore, it is not wise to rely on the selective "respiratory sparing" properties of any of the muscle relaxants now available. Instead, adequate respiration should be assured by manual assistance of respiration by the anesthesiologist when there is a possibility that voluntary respiratory activity may not be adequate.

Variation Due to Relaxant Drug

Most drugs administered primarily for the production of skeletal muscle relaxation contain quarternary ammonium groups and exert their muscle relaxing effects by altering the normal physiological processes involving acetylcholine at the myoneural junction. Since acetylcholine is involved in the normal functioning of other parts of the body, it is also reasonable to expect the muscle relaxants to alter these other functions. In fact it is difficult to explain pharmacologically why the actions of the muscle relaxants are so selective for the myoneural junction.

Paton[16] offered convincing evidence that muscle relaxants are effective by two types of action: (1) A competitive, blocking or antidepolarizing action whereby the relaxant drug is constantly competing with acetylcholine for attachment to the theoretical receptor, as exemplified by d-tubocurarine, and (2) a depolarizing stimulating action whereby the attachment of the relaxant drug to the receptor results in a prolonged effect similar to that produced by acetylcholine. Decamethonium is an example of the depolarizing type of drug. No drug acts purely by either of these types of action in all circumstances and most drugs exhibit a mixture of the two types of action. This led Hunter[14] to suggest that instead of dividing muscle relaxants into two hard and fast groups according to types of action they should all be considered as possessing the same properties but in varying degrees. He compared the muscle relaxants to rungs in a ladder at one end of which are the depolarizing relaxants which stimulate before they inhibit and at the other end the competitive drugs which rarely cause stimulation before inhibition.

The effects of various muscle relaxants on respiration has already been referred to in the sections of this presentation dealing with variations due to species, individuals, and muscles. In addition certain muscle relaxants cause a release of histamine which may result in contraction of bronchial muscle and decrease in pulmonary ventilation. D-tubocurarine is known to cause a release of histamine and for that reason it should be used with caution in patients who have asthma. Other relaxants with a competitive type of action possess the ability to cause release of histamine in varying degree. The depolarizing type of relaxants such as decamethonium and suxamethonium are unlikely to cause release of histamine and therefore they may be used for most

patients with asthmatic tendency. The value of antihistaminic drugs to counteract the effects of histamine released by muscle relaxants is uncertain. Paton[16] pointed out that in general the antihistamines have proved ineffective against histamine liberators such as morphine, meperidine, atropine and the trypanocidal diamidines. On the other hand Goodman and Gilman[11] concluded that the antihistamines are of value if administered before the muscle relaxant is administered.

Very little has been said about the effect of muscle relaxants on the dynamics of circulation. In man the doses used to produce a moderate degree of skeletal muscle relaxation generally have little effect on circulation. In animals larger doses produce more definite effects on circulation because even though the neuromuscular junction is more sensitive to these drugs, the transmission of nerve impulses at other sites may be altered by high concentration of the drugs. Relaxants may affect circulation by alteration of parasympathetic control, alteration of sympathetic control or release of histamine. Guyton and Reeder[12] in studies using dogs compared the sensitivity of parasympathetic and sympathetic nerve transmission with the sensitivity of the gastrocnemius muscle to Intocostrin.® To block the parasympathetic ciliary ganglia and cardiac vagal endings, 1.5 times the gastrocnemius-paralyzing dose was needed. To block the sympathetic ganglia supplying the splanchnic blood vessels and the heart required, respectively, 5 times and 10 times the gastrocnemius-paralyzing dose. From this it is evident that the muscle paralyzing dose of d-tubocurarine, which is the active principle of Intocostrin, is only slightly less than the dose which inhibits the parasympathetic activity but much less than the dose needed to inhibit the sympathetic ganglia. Dimethyl d-tubocurarine is a less potent ganglion blocking agent than d-tubocurarine. The fall in blood pressure caused by the rapid intravenous administration of large doses of d-tubocurarine is probably due to the release of histamine with peripheral vasodilatation rather than to autonomic ganglion block.[11]

Gallamine (Flaxedil®) has less sympathetic ganglion blocking action than d-tubocurarine but exerts a selective atropine-like action on the heart and causes sinus tachycardia. No such parasympatholytic effect occurs on other structures such as blood vessels, eyes and salivary glands. Muscle relaxing doses of gallamine protect the heart against the ventricular arrythmias associated with administration of epinephrine during anesthesia produced with hydrocarbons.[11]

Benzoquinonium (Mytolon®) has a parasympathetic action due to its anticholinesterase activity which is about one-fourth that of neostigmine. The expected effects are bradycardia, salivation, gastrointestinal colic, cardiac extrasystoles and, rarely, bronchospasm. Large doses of atropine are necessary to counteract these effects. The use of benzoquinonium is contraindicated in patients with respiratory disease or atrioventricular or intraventricular conduction block.[11]

Laudexium (Laudolissin®) is about one-fourth as active as d-tubocurarine in causing ganglionic block.[14]

Decamethonium is less than one-fifth as active as d-tubocurarine in causing ganglionic block. Paton[17] showed that the intensity of action of decamethonium is inversely proportional to the flow of blood through the structures being studied and surmised that inhibition to action by the drug in the ganglion may be associated with the connective tissue sheath and its effect on blood flow.

In light of its initial stimulating action at the myoneural junction it is not surprising that suxamethonium may also stimulate autonomic ganglia. Doses larger than those required for neuromuscular block may depress the autonomic ganglia and cause cholinergic response in smooth muscles and the exocrine glands.[11] Johnstone[15] noted that suxamethonium causes bradycardia in 32 per cent of humans. Within a few minutes the bradycardia is followed by an increase in cardiac rate, or, if atropine is given intravenously, the bradycardia is abolished within 20 seconds. Johnstone reported upon four patients in whom the administration of suxamethonium resulted in marked bradycardia and serious fall in blood pressure.

Variations Due to Dose of Relaxant and Effects of Other Drugs

In monkeys, small doses of decamethonium first paralyze the tibialis muscle while the soleus muscle is less affected. If the dose is repeated several times, the effect on the tibialis decreases while that on the soleus increases, so that it is possible, with the proper total dose, to paralyze the soleus and have the tibialis little affected. The same can be accomplished in cats with d-tubocurarine.[18]

In man a four-fold increase in the smallest dose of d-tubocurarine which will affect the most sensitive muscles will result in complete paralysis and apnea.[17] Mention has already been made that in dogs a five-fold increase in the muscle paralyzing dose will block the sympathetic ganglia supplying the splanchnic blood vessels and a ten-fold increase will block the sympathetic ganglia supplying the heart. Provided adequate artificial ventilation is maintained, the effects of doses of this magnitude of d-tubocurarine are reversible in dogs, but 20 times the apneic dose becomes lethal in spite of continuous artificial respiration. According to Cole[6]

it is possible that during these experiments death from overdosage was due to histamine effects, since gastrointestinal hemorrhage was a constant finding and death was ascribed to alteration of the cardiovascular system.

Not only may the effects of muscle relaxants vary with the dose administered but the effects may also be altered by other drugs which are active simultaneously. The proper dose of anticholinesterase will relieve the neuromuscular block caused by the competitive type of relaxants. Large doses of an anticholinesterase like neostigmine can reduce muscle contractions produced in rats by a rapid rate of stimulation and this muscle inhibition can be partially restored to normal by d-tubocurarine.[4]

Ether and cyclopropane enhance the effect of d-tubocurarine but may decrease the effect of decamethonium. An average dose of d-tubocurarine is more likely to cause a decrease in blood pressure when administered to a patient under moderately deep ether anesthesia than when administered to a patient under light barbiturate anesthesia. Guyton and Reeder[12] found that a dose of d-tubocurarine which was fatal to a dog when given rapidly, was safe when given over a 10-minute interval. Hexamethonium, which is noted for its ability to block autonomic ganglia, also exerts a minimal blocking effect of the competitive type at the neuromuscular junction. It can produce head-drop in rabbits, and it potentiates the effect of d-tubocurarine.

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Muscle Relaxants

Their Use and Abuse in Anesthesia

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• Probably the most widely used anesthetic today is the intravenous-inhalant-relaxant combination. The relaxant drugs are the key to this combination. Lack of knowledge of the pharmacology of these drugs, their effect on circulation and respiration and of the physiology of respiration can seriously abuse and impair the evident value of this method. It should not be used routinely to the exclusion of equally valuable techniques that might serve better in some circumstances.

LUMBAR PUNCTURE AND VENIPUNCTURE have long been considered simple procedures easily within the abilities of most interns. A corollary to this "axiom" is that interns may be permitted to take and do readily accept the responsibility of giving anesthetic agents intraspinally and intravenously.

Recent criticism of spinal anesthesia and wide publicity given to a relatively few complications with subarachnoid block have taken this method out of the hands of the untrained and inexperienced.

Partly because of this decline in popularity of spinal anesthesia, partly because of the increased popularity of the Bovie electrosurgical unit, but mostly because it is so easily given and so pleasantly received, intravenous anesthesia has waxed steadily in esteem not only in medical but in nonprofessional quarters as well.

When the ultra-short acting barbiturates were finally effectively developed, they were rapidly accepted. The wise addition of oxygen and nitrous oxide mixtures helped to maintain them in general use, but it was the introduction of d-tubocurarine that truly established the place of this method in medical practice. The intermittent injection of small increments of narcotics throughout the anesthetic period completed the technique.

There is no question that this barbiturate-relaxant-inhalant-narcotic combination has become in the short space of fifteen years the predominant method of anesthesia in the United States. It is a valuable, reliable, precise orderly technique with almost too broad applicability. Without the relaxants, the technique would have certainly a much smaller—although not minor—role in contemporary anesthesia. With curare and the other relaxants it has become famous—and infamous.[1]

There may be profit in exploring some of the reasons for infamy. That "curare" is *per se* responsible for the large number of so-called "anesthetic deaths" attributed to it is impossible to believe. This is not to deny that there have been a number of "curare deaths," but some investigators believe that it is possible there were mistakes in technique or judgment by the anesthetists in some cases. In addition it is possible there have been many other errors of commission or omission which were not fatal or perhaps even debilitating. Hence it is well to give attention to some of the things that may have been done that should not have been done and to things that should have been done but may have been neglected.

To begin with, the successful use of the whole technique requires more knowledge and ability than that needed for successful venipuncture. And even the ability to do venipuncture acceptably is not shared by all the votaries of this method of anesthesia. There are a few simple principles, the mastery of which should be required of anyone planning to administer drugs intravenously.

A fact often overlooked is that once these drugs are injected they are irrecoverable. In the main, metabolic processes must be relied upon for their detoxification or elimination. If plasma pseudocholinesterase is abnormally low, as it might be in patients who have been bleeding profusely, or who have been exposed to certain agricultural poisons, the recovery from succinylcholine injection may be very prolonged. Edrophonium should be used to counteract d-tubocurarine, but it must be remembered that it is a short acting drug and sometimes unreliable, especially when dealing with relatively large doses of curare.

This of course means that the drug and dosage must be chosen to fit the individual case. Yet a timid approach with repeated small doses is undesirable, for one can get into trouble easier with too little curare than with too much.

From the Samuel Merritt Hospital, Oakland 9.

Part of a Symposium on Muscle Relaxants. Presented before the Section on Anesthesiology at the 84th Annual Session of the California Medical Association, San Francisco, May 1-4, 1955.

The relaxants are divided generally into two types: (a) Those causing muscular paralysis by preventing depolarization of the motor end plate by a nerve impulse and (b) those preventing repolarization after the impulse has been discharged. In general, the former are slower of onset, longer of action and less rapidly eliminated. They can be antagonized to some degree by prostigmine and its homologues. Of these, d-tubocurarine is the most useful. The methylated curares, although effective in small dosage, have no real advantage. Gallamine triethiodide is reputed to be less toxic than d-tubocurarine, is readily eliminated in the urine, has no histamine action (although the author has never been much impressed with this feature of d-tubocurarine) and does not cause autonomic blockade or vascular collapse. It is perhaps easier to intubate when Flaxedil® rather than d-tubocurarine is used. But gallamine does increase secretions and it causes tachycardia which can be confusing.

Decamethonium and succinylcholine, the depolarizing agents, are quickly effective and rapidly eliminated, and therein lies their chief advantage. Both are used in combination with d-tubocurarine. However, experience has shown that the administration of decamethonium and d-tubocurarine together, at least in very ill "toxic" patients, may cause persistent and consequently fatal apnea.

Decamethonium is the ideal agent for use when relaxation for intubation only is desired or where periods of 15 minutes or less of relaxation are required. But beyond this, it has little value.

Since succinylcholine is actually a pharmacologic antagonist to d-tubocurarine, the use of these two together is technically illogical. However, from a practical clinical standpoint, they can be used together even in the same syringe. Preferable practice is to use succinylcholine throughout as a drip or to use d-tubocurarine after the initial dose of succinylcholine has been destroyed.

When succinylcholine is used as an aid for intubation of patients having operations about the head and neck, it is common for a patient to complain afterward that "someone sat on my chest" or "kicked me in the belly" during the operation. This phenomenon is apparently secondary to the muscular fasciculation observed after the injection and is, to the author at least, a very real limitation upon its use.

These drugs, although acid in reaction, can be mixed with alkaline pentothal solutions in so-called Baird's or Clark's mixtures. The purpose of this combination is to reduce the required dose of thiopental and consequently lessen postoperative depression. In many cases it serves that purpose, but often an overdose of one drug must be given to get the desired effect of the other. Therefore, it is better to use separate syringes and give the calculated dose of each drug rather than predetermined routine combinations.

Many physicians use curare as an analgesic in spite of the fact that very early it was determined that it has no analgesic properties.[2] Differentiation must always be made between the need for additional muscular relaxation and additional anesthesia. The relaxants should be used for one and the narcotics for the other, but not the relaxants for both. It is possible to so relax a patient that he cannot complain of pain, but to do so constitutes abuse of a valuable drug.

Relaxants are just what the name implies. Respiratory muscles have the fortunate quality of being most resistant to the effects of curare and similar compounds. But some degree of interference with respiration must always be assumed when this combination of drugs is used in clinical anesthesia. They are all respiratory depressants excepting nitrous oxide. If ether is used, it of course acts synergistically with curare.

Too often ventilation is inadequate either because of ignorance or carelessness on the part of the anesthetist. Simply placing the patient in an oxygen-rich atmosphere does not insure a high arterial pO_2. And when ventilation is insufficient to maintain normal arterial tension, there is also insufficient carbon dioxide elimination. And there it is—hypoxia plus hypercarbia equals asphyxia.

On the other hand, overly vigorous, constant "bagging" of the patient can be almost as deleterious either by filling the stomach with air or interfering with circulation.

Furthermore, an endotracheal tube must not be looked upon as the whole solution for this problem. While it is perhaps the most valuable tool in anesthesia, after all, sore throat, dental injury, cut lips, nasal hemorrhage and laryngeal granulomas do sometimes result from use of the tube.

The partial autonomic blockade produced by d-tubocurarine can be a desirable effect, but also it can result in a fall in blood pressure. Hypotension following induction of anesthesia with curare and thiopental is not uncommon, especially if rapid intubation is accomplished. Probably in the majority of patients this is of no consequence; but in a certain few, particularly debilitated or chronically ill elderly patients, it can be fatal.

During the past two decades the rapid evolution of the practice of anesthesia, amounting almost to a revolution, has brought about so many changes that now it seems desirable to speak of the practitioners of this art as anesthesiologists. An anesthesiologist may be described as a practicing physiologist and pharmacologist. Unless he knows well the effects and uses of the relaxant drugs, he is not entitled to

use either the appellation for himself or the drugs in his practice.

Also, one who calls himself anesthesiologist should be master of all techniques used for the production of anesthesia and analgesia. His choice of method and agent should be dictated by all factors operative in any given case and should not be limited by personal preference stemming from lack of knowledge or absence of skill with an alternative technique. All too often, through habit, carelessness, mental stagnation or trepidation, a method or a particular anesthetic agent—cyclopropane or ether, for instance—is not used even though it may be distinctly indicated in a given case.

To be sure, in the majority of cases the balanced intravenous-inhalant-relaxant method serves well if the limitations of the method in general and of the individual drugs in particular are constantly kept in mind. But in many instances it will not serve adequately, and failure then to select the agent and method that is indicated is just as much abuse of the relaxants as is improper dosage or inadequate support of the patient.

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Poliomyelitis Vaccine

A Report on Field Trials in Southern Alameda County in 1954

THOMAS R. PERDUE, M.D., and JAMES C. MALCOLM, M.D., San Leandro

• *Southern Alameda County was the only area in California to take part in the 1954 nationwide field trials for testing poliomyelitis vaccine. Besides the contribution made in evaluating the vaccine, other benefits were:*

1. Participation contributed to the control of a serious communicable disease.

2. Inoculations of vaccine during the field trials in all probability prevented some cases of paralytic poliomyelitis among children in southern Alameda County.

3. The community became better informed about poliomyelitis and more interested in the local health department.

4. Local physicians had an opportunity to contribute to important research and to give a valuable community service.

5. The staff of the Alameda County Health Department became better informed and better prepared for any future responsibilities in poliomyelitis immunization programs.

Other conclusions reached as a result of participation in the 1954 field trials are that the initial planning of the study was hasty and not sufficiently representative of medical and administrative thinking. If the trials had been planned for 1955 instead of 1954 there would have been sufficient time for research to be completed, professional information to be assured and for sound design of study.

GREATLY ACCELERATED RESEARCH in the field of virus diseases in recent years has led to a much better understanding of epidemiologic factors, particularly with regard to poliomyelitis. Great sums of money have gone into intensive studies of that disease, many directed to the ultimate prevention of it or of its paralytic consequences. In fact for a time knowledge accumulated more rapidly than it could effectively be disseminated. Hence the pronouncements in the autumn of 1953 that a trial vaccine was ready for large-scale testing—that, in fact, plans were already well laid for such testing by the National Foundation for Infantile Paralysis—came as a surprise to many physicians.

It seems clear that the studies of Jonas Salk did certainly justify large-scale testing. Few will question, however, that nationwide field trials, as proposed for the spring of 1954, encountered many obstacles as a result of the rush to prepare for them.

It was obvious that an undertaking of this size could be carried out only by local health departments. Plans were such that only certain areas in the country could be considered. The following factors were the basis for possible selection: (1) A high incidence of poliomyelitis among children in the first, second and third grades of school; (2) a large population in these age groups selected for the study, and (3) a well-organized local health department with an interest in the study.

Although some technical information had been published in a few professional journals (a greater amount of publicity had appeared in the lay press) many questions remained to be answered. Virologists, epidemiologists, health officers and practitioners hastened to ask them. These questions had to do with the following:

1. *Safety of the vaccine.* Was the live virus altered in such a way that it could not produce disease? Was kidney tissue a safe element, or was there danger of nephrotoxic effects?

2. *Potency.* Could this particular vaccine reasonably be expected to protect against paralytic poliomyelitis?

3. *Biologic assay.* What procedures were reliable?

4. *Intervals between injections.* What schedule should be used?

5. Was aqueous vaccine likely to produce immunity as good as that produced by an adjuvant-base vaccine?

6. Follow-up and evaluation plans.

7. Administrative arrangements for carrying out the trials.

8. Was it reasonable to believe that solid immunity could result from inoculation of killed virus?

It soon became obvious that although some of these questions could be answered satisfactorily at the time, others could not. It was evident that rather detailed field trial plans had been formulated before

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some of these questions could be answered, and before all the necessary research data had been gathered. But the additional data were forthcoming, and did lend support to the plans. That these results were known at such a late stage and that they were further delayed in their circulation, however, points up an important problem encountered in the 1954 Field Trials. Much of this type of difficulty would have been avoided had the early planning been more representative of health department thinking. And many of the questions about the vaccine might well have been resolved even before plans for an extensive trial were undertaken.

It became clear that the country was in the midst of hurried plans for field trials before the great majority of practitioners and health officers could become well informed about the vaccine itself. There were more than a few physicians who were understandably confused on the subject. But the field trial plans continued, centered on nationwide testing in selected areas. Children in the second grade of school would be injected with aqueous vaccine containing killed virus of the three known types. First and third grade children would serve as uninoculated controls. The trials would involve perhaps 2,000,000 children, and the inoculations would be given according to this schedule: the first on zero day; the second on day seven; and the third, or booster injection, on day thirty-five. About 2 per cent of the children inoculated would also have blood specimens drawn for antibody studies before and after the series of injections. Inoculations were to begin early in the spring and be completed before school was over. Areas for testing were to be proposed by state health departments and approved by the National Foundation for Infantile Paralysis.

PLANS FOR FIELD TRIAL CHALLENGED

Although many states accepted the field trial plan as originally proposed, others raised serious questions:

1. Would the study method proposed give the conclusive answers sought?

2. Were the procedures adequate to assure safety of the vaccine, and

3. Were adequate provisions being made for follow-up and evaluation?

California, in particular, insisted that a sound trial would necessarily include use of a placebo, and insisted, further, that satisfactory answers be obtained to the questions regarding safety of the vaccine before the state would agree to participate. It was only in February, after many weeks of nationwide publicity about the trials, that satisfactory information was made available to California which permitted a sound decision to be made. On the recommendation of an Ad Hoc Advisory Committee, the State Department of Public Health agreed to participate, and this decision received the approval of the State Board of Health.

There were several areas in the state considered suitable—among them, San Diego County, a portion of Los Angeles County, and southern Alameda County. Whether from lack of funds, early rise in incidence of poliomyelitis, or from lack of community interest, all areas but southern Alameda County ultimately indicated they could not take part. Southern Alameda County remained under consideration only because of a keen interest on the part of the community, and a sincere desire on the part of the local health department staff to engage in this program. The decision by the Alameda County Health Department to participate was reached only after considerable efforts had been made to get the necessary information—and only after thorough analysis of the meaning participation would have. The great public interest, and the opportunity to provide an unusual community service were factors of obvious importance. And, of course, the fact that Alameda County could make a contribution to the nationwide study was of no little consequence.

Designation of the southern part of the county by the State Department of Public Health as a trial area followed, and active local planning got under way. The county health officer called together a group made up of representatives of the medical profession, of the local chapter of the National Foundation for Infantile Paralysis, of school systems, of Parent-Teacher associations, of newspapers and the staff of the county health department. A representative of the State Department of Public Health who attended presented information about the trials in some detail. After discussion ended, the opinion of the group was asked for. It was quickly forthcoming in a motion endorsing local participation and promising full cooperation from those present. The group requested that the county health department proceed with the planning and ask for whatever help would be needed.

A small planning group was quickly formed, composed of the county health department staff, with a representative from the local chapter of the National Foundation for Infantile Paralysis, and a member of the State Department of Public Health. Meetings were held twice weekly at regularly scheduled times. Early meetings were geared to the following objectives: (1) Approval by the local medical societies, and agreement by their members to participate in the trials; (2) interest among school personnel; (3) interest among parents and a desire to take part, and; (4) a well-informed local health department staff willing to give the extra time and effort needed for a successful job.

Professional interest already abounded, and active local medical support was forthcoming as soon as adequate information was made available. Not only did local physicians approve participation, but they volunteered to give the injections in the schools. Early talks to local physicians by the health officer, and by members of the State Department of Public Health were instrumental in providing information and in gaining support. Later, printed information of a technical nature was circulated by the health department to Alameda County physicians in an attempt to answer their many questions.

This material presented a rather comprehensive idea of the preparation, testing and use of the vaccine, and local practitioners greatly appreciated it, for they had no other easily available source of such information.

Interest of school personnel was necessary, since the trials were based on their active participation. So an early meeting was arranged with the 30 school administrators in the area, and current plans were presented. Their endorsement resulted, and each agreed to request the approval of his respective school board. After many approvals had been obtained, one school board raised the question of legal liability, and asked the opinion of the district attorney. A preliminary statement from the district attorney's office made it plain that public schools lacked the authority to take part in the study, and, further, pointed out that the injections could be given in the schools only after regular school hours. It appeared, for several days, that all plans had been in vain, but in a final legal opinion a way was found. Injections could be given during school hours, but school personnel could take no part in the trials. The first big hurdle was cleared.

INFORMING THE PUBLIC

The public desire for information was satisfied largely through talks to parent groups by physicians of the county health department and by local practitioners. Newspaper and radio coverage were also extensive. In the later stages, printed information prepared by the local health department was sent to all parents of first, second and third grade children. Public health nurses, as well, contributed a great deal toward public education.

Interest within the health department was at a high pitch, and early efforts were concentrated to provide a well-informed staff, each member with an adequate understanding of the trials. Special educational meetings were held for the nursing staff early in the planning, and at a later meeting the entire staff heard the plans explained by Dr. Robert Korns, a member of the Vaccine Evaluation Center Staff. Minutes of planning meetings were circulated so the whole staff could keep abreast of developments.

VOLUNTEER HELP

Agreements were reached with the local chapter of the National Foundation for Infantile Paralysis regarding financial support, and the chapter also agreed to be responsible for recruiting the volunteer help needed.

Because of the public enthusiasm for the study, volunteer recruitment was no great problem. The forms that parents were required to fill out giving permission for vaccination were prepared, and sent to parents, and were returned. Clinics were scheduled, and time for the injections approached. But there were serious doubts that the vaccine could arrive in time. Final safety testing had to be completed and the lots officially approved before they would be released for shipment. Again, plans had to proceed without assurance they could be carried out. Physicians were assigned to clinics and notified of the work schedule. Recorders were trained, volunteer nurses recruited and clinic teams formed. But the vaccine was further delayed. It was not until April 25 that any vaccine was released, and only the afternoon before injections were to begin that shipment to California started. At the very last moment the National Foundation had decided against California participation, for reasons still not clear. It was only after urgent assurances from the state health officer and from local National Foundation for Infantile Paralysis chapter officials that the vaccine was put on its way.

It did arrive, and, quite dramatically, just two and a half hours before injections were to begin. But the clinics operated as scheduled, the injections were completed, and the first easy breaths drawn.

By June 10, 1954, 7,166 children had received three injections each—half of them with vaccine, half with placebo—all identified simply by a code, the key to which was known only at the Evaluation Center in Michigan. A hundred local physicians and some six hundred other volunteers had taken part. The entire staff of the county health department, including all sanitarians and clerical personnel, had been directly involved. Clinics were held May 5 and 6, May 12 and 13, and June 9 and 10, in 90 different schools.

The first part of the study was over, but important responsibilities remained. To give any meaning to the trials, careful follow-up and good evaluation had to be assured. Blood studies for antibody titrations were to be made on all family members in any family in which there was a case of poliomyelitis and a child of the study age group. And stool specimens were to be collected for virus isolations in similar circumstances. Uniform diagnostic criteria were to be applied, and prompt reporting was a necessity. Muscle grading examinations were to be arranged for children in the study ages who con-

tracted poliomyelitis. Promptness was necessary in reporting cases to the Evaluation Center, as well as completion of attendant epidemiological histories. Responsibility for the follow-up was shared with the State Department of Public Health. The period of follow-up extended from May 10 through December 31 of 1954.

Results of the follow-up now reveal that a total of ten cases confirmed as poliomyelitis occurred during this time among children in the study age group in southern Alameda County. Seven of these ten cases were among children who did not receive any injections. The remaining three cases all occurred in children who had received the placebo.

The final results of the nationwide trials became known April 12, 1955, and need no repeating.

A review of the participation of southern Alameda County in the study brings out the following conclusions:

1. Initial planning of the study was hasty and not sufficiently representative. If the trials had been planned for 1955, instead of 1954, there would have been sufficient time for research to be completed, professional information to be assured, and for sound study design.

2. Public health authorities in many areas were willing to accept without argument a trial originally designed on an unsound basis. Save for the insistence from some states, no placebo trials would have been conducted, and the results could not have been so conclusive.

3. Participation in the study contributed to the control of a serious communicable disease.

4. Inoculations during the field trials in all probability prevented some cases of paralytic poliomyelitis among children in southern Alameda County.

5. The community became better informed about poliomyelitis and more interested in the local health department. Increased public respect for the health department resulted.

6. The 1954 Field Trials provided the first real opportunity to work with the local chapter of the National Foundation for Infantile Paralysis, and proved in still other ways that teamwork was possible.

7. Local physicians had an opportunity to contribute to important research, and to give a valuable community service.

8. Members of the staff of the Alameda County Health Department are better informed, more interested, and have greater self-assurance for future undertakings.

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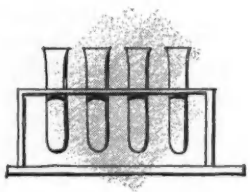

A Medical Student Looks at Blue Shield

CARL B. YOUNGER, North Hollywood

AS THE PHYSICIAN OF THE FUTURE, the medical student of today looks at the present as he reads of the past and dreams of tomorrow. His observation of the present is preparation for his participation in the future. He relates his personal struggle to the strivings of the profession. Professional problems become personal problems. And he knows that when he becomes a functioning part of medicine, personal problems will then be professional problems. Therefore, he is more honest with himself if he analyzes a problem that will soon be his with respect for his own feelings instead of attempting to achieve objectivity through superficial elimination of subjectivity. It is with this attitude that this medical student looks at Blue Shield.

A SCIENCE OF SERVICE

Medicine is a science of service. It was created by man, for man, to protect man's most precious possession, life. How to serve his fellow man most effectively is the universal challenge of medicine. It is the personal goal of the physician. In a democracy dedicated to the proposition that all men have the right to equal opportunity, the proportions of the challenge are enormous.

Accepting the challenge as a personal problem, the medical student asks of himself, how should this be met?

In answer, he focuses first on the primary participants in the practice of medicine, the physician and his patient. Their relationship is the essence of medicine.

He narrows his scope of observation and considers this relationship in terms of the patient. First and foremost, the patient has the right to medical care when he needs it. Neither the quantity nor the quality of care should be solely dependent on the patient's economic status. For this care to be fully effective, anxiety stress which can complicate or create illness must be kept to a minimum. Doubt in the doctor and concern over cost are frequent causes of preventable anxiety. If the patient finds that he lacks faith in his physician, he should have the right to choose another in whom he can have confidence. He should be able to direct all of his energy toward getting well and not have it consumed by worry over the bill.

The primary responsibility for the physician-patient relationship rests with the physician. It is essential that he be able to concentrate his skill and concern on each patient as an individual. He must have the freedom to decide, on the basis of his knowledge and experience, how best to treat every person who comes to him for care. He must have the opportunity to establish the closeness necessary for communication. He must be in a position where he is free to serve the needs of the patient and practice in a manner that is satisfying to himself.

The relationship of physician and patient that is based on mutual respect benefits both and forms a solid foundation for sound medical practice.

This, then, is the answer for the student.

But how have others answered the question in practice?

Since early in the history of medicine post-paid private practice has been the dominant form of medical service and it continues to the present day. This is a system whereby a patient chooses a doctor when in need of medical care. The care is prescribed for the patient by the physician. The patient is billed by the physician according to the services rendered. With complete freedom of choice, the patient may select a doctor in whom he has confidence. He has the right to solicit different or additional medical advice. These factors, however, are limited by the condition of his pocketbook. The request for needed medical care is frequently postponed or never made because the patient may feel that it is easier to be sick than to worry about the doctor bill. His freedom of choice is limited by his income tax bracket. He may lack confidence in his doctor because he *can* afford him. If more help or treatment is indicated, he can get it *if* he can pay more for it.

PATIENT-PHYSICIAN RELATIONSHIP

The core of private practice is the patient-physician relationship. The physician is able to serve his patient with skill and understanding, since he is free to devote the time he feels necessary to the individual patient. He is free to prescribe the therapy that his knowledge and experience indicate as appropriate. However, as a human being, the doctor is concerned about his own economic welfare. Therefore, of necessity, the patient's ability to pay is a factor in their relationship. The concern

Mr. Younger, a medical student (Class of 1958) at the University of California at Los Angeles School of Medicine, won first place in the California Blue Shield essay contest and second place nationally.

of a patient over his projected bill is obvious to the physician. It is important that the physician relieve this anxiety in order that he and the patient may work together on the primary problem, the patient's illness. The time consumed in relieving this anxiety could better be devoted to relief of the illness. His prescription for medication or therapy may have to be bounded by how much the patient can pay, and not necessarily by what would be most beneficial.

THE "PRACTICE FOR PROFIT" BARRIER

Another form of service is found in the prepaid group practice for profit medical plan. In this type of plan, integrated groups of specialists are brought together under one roof. Potential patients subscribe to the services of these doctors for a fixed fee, usually payable monthly. The patient has the right to medical care when he needs it, according to the terms of the contract. Potentially, the services of every physician in the organization are available to him. The prepaid factor of this plan helps to relieve the patient's anxiety regarding finances. The services of this type of plan are limited to those living within the area where a major facility is located. This particular plan functions principally as a business enterprise. Practice for profit is the primary purpose of the organization. All other goals are subsidiary.

The member patient's choice of a physician is limited to members of the organization. It is frequently further limited by organizational policies or clerical procedures. For example, an emergency request for Doctor "A" is answered by the switchboard operator with, "So sorry, only Doctor 'X' is on call tonight." A call at the office may provide the information that Doctor "B" is no longer with the organization and Doctor "C" has no available appointments, but Doctor "Y" has a cancellation. As the patient passes from one to another on this medical assembly line, he begins to feel more like a part than a person. This recipient of conveyor belt care gets lost in the shuffle of charts and routines. He is a patient that passes through, not a person for whom the physician cares, for whom he works and to whom he devotes the summary of his years of experience to help. There is little opportunity for the patient to feel secure through his relationship with the physician.

As an employee, the physician is more responsible to the organization than to the patient. The physician becomes a servant of profit. His practice is regimented rather than self-regulated. The unique professional challenge of medicine is gone. The physician's identity is lost. He is a man with a job to do.

Compulsory government-controlled health insurance and socialized medicine have been suggestions made by some. Cost of care to the individual would seemingly be minimized, but would, of necessity, be reflected in much higher taxes to all. The American system of free enterprise would be corrupted by such a plan involving the sacrifice of incentive, initiative and individuality. Without these essential elements, the profession of medicine, as the healthiest nation in the world knows it today, would cease to exist.

Blue Shield, a nonprofit organization, conceived and controlled by the medical profession, offers still another plan in the form of voluntary health insurance. In Blue Shield, a subscriber insures medical treatment in advance by depositing small premiums at regular intervals. When in need of medical treatment, he consults a physician of his own choice, who is paid entirely, or in part, directly from the Blue Shield fund. Relieved of financial stress, a patient will not put off seeing his doctor at the first symptom of illness. This will enable the physician to work more effectively with him. Secure in the knowledge that medical care is available when he needs it and assured that it is not beyond his means, the stress of illness is not increased by anxiety over post-emergency costs. A Blue Shield subscriber knows that he himself may choose the physician in whom he has confidence. Thus the personal relationship so necessary to healing is on a stronger basis because the physician he goes to see as a Blue Shield member is *his* doctor.

ADVANTAGES TO THE PHYSICIAN

The physician who uses Blue Shield service develops and regulates his own practice. Initiative is an asset, not a liability. Personal identity is not lost. Professional integrity is maintained at his own standards. As in all private practice, the physician's primary responsibility is to the patient that he serves. Since the practice is his own, he is able to have the type of relationship with his patient that he desires. A Blue Shield subscriber is *his* patient and the personal satisfaction of purposeful practice is his. When a Blue Shield patient comes to the physician, the fee communication barrier is lowered because the Blue Shield schedule of fees provides the basis for opening discussion.

Essentially, Blue Shield serves as a reservoir of funds to which the patient deposits regularly and from which the physician withdraws when he gives treatment. It is operated solely for the benefit of the patient and the physician. No profit-seeking third party is involved. It is not without flaws, but it is flexible. Changes, as needed, can be made through the physicians who direct its operation.

This student has compared Blue Shield with other forms of practice on the basis of his own standards

of service. He has found no plan without merit, and of course, no plan that is perfect.

He has found in Blue Shield a plan that preserves the vital personal relationship between the patient and physician, provides a professionally led program of competent care, protects the patient from the financial catastrophe of illness and injury, promotes physician incentive and initiative and presupposes progress by a flexible form of operation.

This student of medicine looks forward to a professional career in which his personal satisfaction will come from his professional ability to help others. Blue Shield fits into such a professional career, helping him meet the challenge of providing medical care for his fellow man.

This medical student today is looking forward to becoming a Blue Shield physician of the future.

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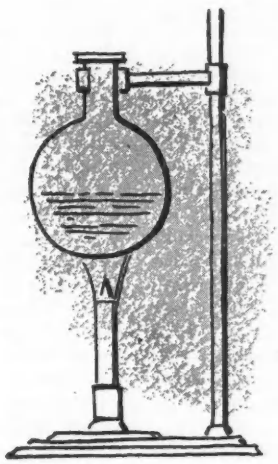

CASE REPORTS

Poisoning by Organic Phosphate Insecticides

ROY C. SMITH, M.D., MORTON KIMURA, M.D., and MAXWELL IBSEN, M.D., San Jose

A NINE-YEAR-OLD Japanese boy, vacationing on his grandparents' ranch, spent about one and a half hours with his grandfather and two teen-age cousins while they were dusting a strawberry patch. The dusting agent used, a 2 per cent adsorption of parathion on a wettable dust, was marketed under the trade name of "Thiondust" to be used in that concentration. It was adequately labeled in English regarding toxicity, precautions and first aid treatment. The label also included instructions for physicians. The distributor keeps on his sales counter illustrated booklets printed in nonprofessional language by the California Department of Industrial Relations containing warnings and instructions in English and Spanish.

The weather on the day the dusting was done was hot and windy. Perhaps because of language difficulties, the adults did not comprehend the dangers involved. The grandfather had a mask which he wore for a short time, then discarded as a nuisance. The nine-year-old boy did not wear a mask or protective clothing.

After the first spraying operation none of the persons concerned had any symptoms.

The second day about two hours were spent in the same manner. On the way home the boy rode alone in the load compartment of the truck with the bags of Thiondust, but it is not known whether or not he was in actual contact.

Shortly afterward, all four began to complain of headache. In the adults, the symptoms did not progress further, but the boy rapidly became acutely ill. His grandmother, at first unconcerned about the headache, soon noticed that he was perspiring profusely. She gave him an enema but before he had expelled it, he seemed to be losing consciousness and she called a physician. He was rushed to the nearest hospital, ten miles away, by ambulance.

He arrived there at 3:30 p.m. in a state of shock, vomiting frequently. The temperature was 99.2° F. The pupils were constricted. The neck was not stiff. Respirations were rapid and difficult. There were no rales. The heart rate was rapid and regular and no murmurs were heard. There were no abnormalities in the abdomen and genitalia. The extremities were cold and sweaty.

Given 0.3 mg. of atropine intravenously immediately on arrival, the patient responded quickly. At 4 p.m. the pupils were dilated and the patient was able to talk intelligently and seemed much better. At 4:30 p.m. he passed a large liquid stool involuntarily and seemed incoherent. The nurse's notes indicate that the pulse was rapid and that there was "mucus in throat." At 4:40 p.m. the nurse wrote, "pupils contracted, eyes twitching, not responding." At 4:50 he was given 0.3 mg. of atropine again but did not respond as previously. Muscle twitching became generalized and the patient was soon in a state of unremitting convulsions. He was given 0.4 mg. of atropine by vein twice more, but with no apparent effect. The pupils remained pinpoint and he was mildly cyanotic, in spite of oxygen by nasal catheter and postural drainage.

At about 8 p.m. voluntary respirations ceased rather abruptly. Artificial respiration and respiratory and cardiac stimulants were used but at 9:05 no heart action could be found and the patient was pronounced dead.

Blood had been taken for routine laboratory examination, and the report on it was: Hemoglobin content, 15.4 gm. per 100 cc.; erythrocytes, 5,290,000 per cu. mm.; leukocytes, 29,900 per cu. mm.—28 per cent stabs, 62 per cent segmented, 9 per cent lymphocytes and 1 per cent monocytes.

At autopsy the following conditions were noted: Congestion and edema of the lungs; subepicardial and subpleural petechiae; postmortem fluidity of the blood; focal atelectasis of the lungs; congestion of the liver, spleen, and kidneys. The pathologist said that the findings are consistent with death by asphyxia resulting from exposure to a chemical agent.

Submitted January 24, 1955.

CASE REPORT NO. 2

The person concerned in the following report was not seen by a physician. The information given here was obtained from the Coroner of Santa Cruz County and the California State Department of Industrial Relations.

A 35-year-old pilot of a crop dusting plane carrying "Vaportone," a powder containing 1.5 per cent tetraethylpyrophosphate (TEPP) was doused with the powder from head to foot when the dust bin flew open at a crash landing after gradual loss of

altitude short of the destination. As he crawled out of the open cockpit he refused help from persons who went to his aid, said he was not injured and would not permit them to call an ambulance. He asked for water, drank it, and then immediately complained of illness and asked for a physician. A moment later he slumped to the ground. He died in a very few minutes.

At autopsy, the only finding of significance was that the respiratory passages were thickly coated with the dust. There were no fractures. The cervical spine was especially examined and found intact. The only evidences of injury were a few superficial abrasions.

An ambulance driver, a mortician and a pathologist all complained of headache and stomach cramps after handling the body.

The Civil Aeronautics Authority found no evidence that the accident had been the result of mechanical failure. Investigators later learned that the pilot had been known to spray the dust over workers when they had not gotten off the field in time. He had been warned against this practice by the California State Department of Industrial Relations. For a few days before the accident he had complained of headache and visual troubles. His employer had urged him to have a blood test but he had refused.

DISCUSSION

The organic phosphate insecticides were developed during the last war by German chemists incidental to a search for war gases. Although at first used only for larger agricultural units, they are now available in small quantities in many garden supply stores and have created a growing public health problem.

The California State Department of Public Health reported 158 occupationally incurred cases of organic phosphate poisoning in 1953—128 of them from parathion. There were five known fatalities. It is probable there were many other cases not reported.

The organic phosphate insecticides now in common use in California are TEPP, parathion (diethyl-p-nitrophenyl thiophosphate), Demeton or Systox (diethoxy thiophosphoric ester of 2 ethyl mercapto ethanol) and Malethion (dimethoxy dithiophosphate of diethyl mercapto succinate).

In pure form they are amber to straw-colored oily liquids, stable at room temperatures.[16] Parathion hydrolyzes very slowly and has a higher degree of solubility in lipids than do the other preparations.[10] These properties, which make it the most dangerous of the group, have also led to its acceptance as the insecticide of choice for most crops. Demeton is a "systemic" insecticide. As it will control pests in all parts of the plants when applied to any one part, it is of obvious value in inedible crops and its use has so far been restricted to cotton. Malethion is the least toxic of the group mentioned.

These compounds are readily absorbed from skin or mucous membranes and are toxic by contact, inhalation, ingestion or injection. Their toxic effect is due to their ability to inactivate cholinesterase. Acetyl choline serves as a chemical mediator for the nerve impulse at parasympathetic synapses. It is normally destroyed within one hundredth of a second by cholinesterase. As a result of this inhibition, acetyl choline accumulates in the tissues, producing effects resembling those of prolonged stimulation of cholinergic nerves.

The effect of a single dose of TEPP and parathion is partly reversible for the first several hours. Repeated doses produce a progressive and largely irreversible inactivation of cholinesterase.[6] Plasma cholinesterase is restored, presumably by the liver, at the rate of approximately 14 per cent of original activity on the first day, 9 per cent on the second day and 2 to 6 per cent on subsequent days until normal levels are restored in about three weeks. Restoration of erythrocyte and tissue activity parallels the rate of erythrocyte replacement and requires about three months (1 per cent per day).[11]

After absorption, the plasma cholinesterase may fall to nearly zero and that of the erythrocytes to below 10 per cent of normal activity before symptoms appear. Symptoms may disappear as the erythrocyte activity increases above 15 per cent of normal.[12] Thus, repeated exposures may lower cholinesterase levels to a dangerous point without producing symptoms; then a subsequent, perhaps mild, exposure may be fatal.

The effects of acetyl choline are called *muscarinic* when the site of action is at glands and smooth muscle and *nicotinic* when it is at ganglia, skeletal muscle and the central nervous system. The earliest muscarinic effects are anorexia and nausea, which may be aggravated by smoking. Soon afterward vomiting, abdominal cramps and excessive perspiration and salivation may occur. Heavy exposure will cause diarrhea, tenesmus and incontinence. The blood pressure tends to rise, the pupils to constrict; and increased bronchial secretion leads to pulmonary edema and cyanosis.

The nicotine-like effects manifest themselves shortly after the onset of nausea and vomiting. At first, fasciculations of the eyelids and tongue are seen. These spread to involve the muscles of the face and neck and become generalized. Extraocular muscle involvement may cause nystagmus.

The earliest central nervous system effects are giddiness, restlessness and anxiety and may be noted even before the onset of nausea and vomiting. Headache and insomnia follow. Severe exposure causes ataxia, disorientation, drowsiness and slurring speech. Coma precedes death.[8]

The muscarinic symptoms are first to appear and they respond readily to moderate doses of atropine. The later occurring nicotinic effects require much larger doses for control.

These facts have led to an unfortunate sequence of events which is well illustrated in many of the published case reports[1, 2, 8, 9, 12] and by the case

here reported. The patient is first seen with nausea, vomiting, excessive perspiration and salivation, and miosis. He is given a "safe" dose of atropine and in a few minutes he is better. The pupils have dilated and the excessive flow of secretions has been relieved. A short time later, however, the more dangerous nicotinic and central nervous system effects come into play and unless treatment is prompt and vigorous the patient is soon dead.

The acute emergency lasts from 24 to 48 hours and the patient must be closely watched.

Atropine is the only known specific medication. It is very effective against the muscarinic effects, but much less so against the nicotinic and central nervous system effects. It can be used in dosage which would be dangerous were it not for the fact that a physiological antagonist is already present in the tissues in relatively large quantities. Two milligrams should be administered when the patient is first seen and this dose should be repeated at least every 15 minutes until atropine effects are noted. It would seem safe to say that as long as the pupils are miotic the patient has not received enough atropine. The only seriously poisoned persons who have survived have received large doses, and in none of the fatal cases thus far reported were such doses given. One patient who lived received 14.2 mg. in the first two hours and ten minutes.[15]

Since peripheral respiratory failure precedes cardiac failure, life can be prolonged and chances of survival enhanced by the use of artificial respiration when indicated. Oxygen should be administered if cyanosis occurs and a clear airway should be maintained by means such as postural drainage or suction. Although bronchiolar spasm also plays a part in respiratory failure, tracheotomy should be done if cyanosis does not disappear in response to these measures. The use of a positive pressure apparatus such as the Bennett machine may be lifesaving. Du Bois demonstrated that animals can be protected against anticholinesterase drugs by atropine. The degree of protection is greatly increased if the animals are also kept under artificial respiration. "Almost indefinite amounts of parathion up to 140 mg. per kg. of body weight were given in divided doses without visible effects to the animal," Du Bois said. He also observed that with doses beyond those required to cause respiratory failure, pronounced bradycardia developed, "the tracing showing a greatly exaggerated pulse pressure suggesting A.V. block."[4] This suggests a possible clinical value in the prophylactic use of Isuprel® (isopropylarterenol) in cases of severe poisoning and a possible danger in the use of digitalis.

Removal of clothing and careful cleansing of the entire skin surfaces should be carried out as soon as the urgent, life-saving measures have been done. Since parathion is hydrolyzed more rapidly by alkali, the use of soapy water with added soda is recommended. If there is any question concerning the possibility of ingestion, gastric lavage should also be done.

It is not safe to administer atropine to an exposed symptomatic patient and allow him to go home unless he can be carefully observed for the duration of the danger period.

Deichman found Buscopan® somewhat more effective than atropine in treating organic phosphate poisoning in rats.[3] So far as could be determined there are no reports of its use in humans.

Johns and co-workers[14] demonstrated that the convulsant effects of theophylline, theophylline-ethylene-diamine (aminophyllin), and chlorotheophylline are increased six-fold by the anticholinesterase drugs. Therefore, use of them should be avoided. Morphine is also contraindicated, for obvious reasons.

Deaths have been reported from contact with parathion in all phases of its manufacture, preparation and field use. The need for protective clothing and masks by workers concerned and the immediate and careful washing of any areas of contact is obvious. The U. S. Department of Agriculture has issued bulletins containing recommendations as to types of protective clothing and respirators. Careful instruction concerning the dangers involved and methods of protection is mandatory. The distributor ought to assume the responsibility of making certain that purchasers who know only a foreign language, are fully cognizant of these facts.

For reasons previously mentioned, a person who is exposed sufficiently to cause symptoms must avoid further exposure to any organic phosphate until the cholinesterase level returns to what is normal for the individual (or levels off if preexposure level is not known). Three weeks is a practical interval where cholinesterase determinations are not available.

The condition is recognizable even without a history of exposure. A combination of miosis with perspiration and excessive bronchial and salivary secretions should suggest it. Blood cholinesterase determinations are useful not only in diagnosis but as a guide to the degree of exposure in handlers. More recently a method for the detection of p-nitrophenol, an end-product in the metabolism of parathion, has been developed and may replace the slower cholinesterase determinations in diagnosis of poisoning by parathion.[18]

Moderate leukocytosis (15,000 to 20,000 leukocytes per cu. mm.) has been a common finding.[8]

The toxic or fatal dose is related to the size of the individual. A child may die from an exposure that will not produce symptoms in an adult. Experiments with rats have demonstrated a far greater susceptibility to the effects of di-isopropyl fluorophosphate in the infant of the species, supposedly due to lower brain cholinesterase.[7] Chamberlin and Cooke[2] reported a five-month-old infant who became seriously ill three and one-half days after the room in which his diapers had been hanging in an open cloth bag was sprayed by a parathion preparation. Children should never be allowed in the vicinity of spraying operations, and these preparations should never be used as insecticides in the home.

The authors know of no reports of ill effects from marketed foods which in California are checked for residues at the wholesale level by the State Department of Agriculture.

Pilots using these products in dusting operations are doubly endangered. The hoppers into which the dust is loaded are usually located in front of the cockpit. If the hopper is not properly sealed, the pilot may have great exposure in a short time. A dosage which would not otherwise be fatal may cause a pilot to lose control and crash his plane.[13, 19]

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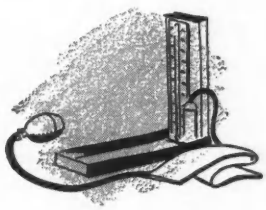

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EDITORIAL

Poliomyelitis Vaccination

SURGEON GENERAL SCHEELE and Associate Director of Laboratories* Shannon conclude their final report "The Public Health Implications in a Program of Vaccination Against Poliomyelitis"† with the statement: "Final decision on the use of vaccine remains the responsibility of individual physicians and health officers."

Millions of words have been written about the current experience with poliomyelitis vaccine. It has been said that not twenty men in the country could successfully negotiate all the ramifications of what actually happened. Few physicians are in a position to have complete knowledge of this entire affair but it is certainly necessary for them to study the facts and conclusions which have been presented in order to arrive at a decision which will guide them in discharging their responsibility for the administration of vaccine. Many theoretical conclusions must be decided by expert virologists but very many of the observations are entirely intelligible to the alert clinician.

The Francis evaluation of the field trials described a carefully planned scientific experiment on a fairly large scale. This report was completely reassuring in the matter of safety, it detailed a convincingly encouraging response in antibody production and supported the belief that a considerable degree of clinical protection was thus established, especially against the severer manifestations of poliomyelitis.

Transition to mass production of the vaccine, approval by the Public Health Service, and institution of nationwide administration were impetuously effected. There was little time or opportunity for examination of the field trial results by those with the ultimate responsibility of carrying out the authoritarian directive for mass immunization. Some protests were heard but many were silenced by the hope that we stood on the brink of an effective control measure for this serious problem. Difficulties which might have been anticipated were not foreseen. Physicians cannot lightly escape responsibility but voices once stilled cannot now be raised too loudly in protest.

Although the Francis Report promised complete safety of the vaccine, it was quickly discovered that under the conditions of routine application this assurance was not entirely borne out. Paralysis occasionally followed vaccination and the time interval of its appearance and localization to the injected extremity paralleled the experience of twenty years ago in which a crude vaccine later found to contain live virus was used on a small scale for similar purpose. A further disturbing development was the appearance of secondary cases of paralytic disease in the families of inoculated children.

These bad effects were most frequent with the product of a single manufacturer but were not encountered in all lots from this source prepared by identical methods nor even in any great number of children injected with the same lot of vaccine. Although most of these unpleasant incidents occurred with vaccine from this single source, other sequelae of persuasive similarity followed the use of vaccines produced by other manufacturers.

Early efforts to explain away these difficulties on the basis of pure chance, or from the use of vaccine during the incubation period of naturally acquired disease, or from the possible provocative effect of any injection in precipitating paralytic symptoms all quickly collapsed and almost every observer was soon convinced that these particular results could only be due to the persistence in the vaccine of some live virus which had escaped the killing effect of formalin.

The mass administration of vaccine was inadvertently a controlled experiment in which paralytic poliomyelitis occurred in numerous patients injected with some lots from one manufacturer, in occasional preparations from at least one other laboratory, and perhaps not at all from still other sources, the observed number of cases being sufficiently great to indicate that the sequelae were owing to essential differences in the vaccine preparations. One of the most convincing items of clinical evidence that live virus must have persisted in some of the preparations was that relatively so many children age one

*Of the National Institutes of Health.
†J.A.M.A., 158:1249, August 6, 1955.

to two years — during maximal susceptibility — should develop the disease following vaccination, the presence of live virus thus being demonstrated in a subject more sensitive than tissue culture or the laboratory monkey. The final bit of evidence was afforded by the isolation of live virus by Gebhardt from a lot of vaccine known to have been used for vaccination in a case in which paralysis followed injection.

A desperate effort was made to pin the responsibility to a single manufacturer—Cutter—but all of the vaccine produced followed carefully prescribed procedure. To date there has been no evidence introduced that there was any failure of conformance with established safety standards in the preparation of any of the suspect vaccine and it seems entirely likely that any discovered defect would have been quickly reported. The inescapable conclusion is that standard methods of production were in some way at fault and that inadvertent departure from these standards was not responsible for impaired safety.

The safety of some lots of vaccine as compared with those which caused trouble may have been due to slight modifications in procedure well within the framework of that laid down for the manufacturer. There was certainly some variation in the actual length of time during which the virus was exposed to formalin. Reportedly the formalin was not finally removed from one preparation which proved safe. Merthiolate was added as a preservative to the product of one manufacturer but when this addition was shown to interfere with the antigenicity of type I virus in the field trials, versine was added to overcome this interference. It has been suggested that the inclusion of Merthiolate was an unsuspected safety factor* whatever its effect on antigenicity. Still another commercial vaccine contained Phemerol, a quarternary ammonium compound not only bacteriostatic (perhaps virocidal) but also a dispersing agent which might afford increased safety through better dilution of occasional surviving live virus particles.

There are extant the opinions of many virologists that stimulation of antigenic response is afforded only by live virus and that the effectiveness of "killed" vaccine depends upon the persistence of at least a very little live virus. Dr. Salk's contribution to the contrary is almost unparalleled. Thus the safety of an effective vaccine as demonstrated in the field trials might depend upon extreme dilution and dispersion of a very few remaining live particles.

Safety requirements have now been severely revised and the assurance of harmlessness is now quite convincing. It remains to be proved that the antigenicity of present vaccine will equal the results reported in the field trials.

Many matters affecting the field trials still bear careful scrutiny:

1. It remains for experience to demonstrate that rise in serum antibodies invariably parallels clinical protection. This seems to be a reasonable assumption and is at least indicated by the field trials, but such a conclusion cannot be a product of pure logic and is arrived at only by the passage of time and continued observation.

2. In only a small number of the persons exposed to poliomyelitis does the disease spontaneously develop, and it is known that many acquire infection without ever showing signs of illness. It is not altogether improbable that those with maximal constitutional susceptibility may by the very ones least protected by vaccination.

3. The Francis Report indicated much less protection in children six years old or younger as the result of vaccination, with an improved response at older ages. It would thus appear that vaccine is far more effective as a booster than as an instrument for basic immunization.

There are many other considerations which one might enumerate and which merit—and will certainly receive—continued study. Live vaccines using avirulent viruses may prove to be the final answer, but for this almost endless research is required. It seems unfortunate that the proposal of Sabin, Enders, and others that avirulent type I virus be substituted for the Mahoney strain (thus being essentially nonparalytic even if surviving formalin treatment) was rejected in the interests of haste.

Mass immunization this year might better have been proposed as a continued experiment to extend the field trials of 1954 rather than being proposed *ex cathedra* as the accomplished method for universal protection. A considerable and sufficient proportion of the public could then have chosen to accept the uncertainties and even the unsuspected risks of a protective measure which offered reasonable promise of success and would then have been better prepared for some degree of disappointment. To the extent that vaccine was given within a restricted age group, controls would automatically be set up in adjoining age groups between which comparisons could be made. In California maximum incidence is from age four to six and comparisons with those vaccinated at age six to eight might afford data of great value.

Should vaccine now be given as it becomes available? Each physician must decide this question himself, for there is now enough information to justify conclusions one way or another. Vaccine need not be impatiently rejected; indeed it must not be, for the careful and scientific studies of our experience to date hold much promise of the eventual development of an innocuous and effective immunizing agent. There is now convincing evidence of the safety of present preparations. Final conclusions regarding antibody response, and clinical protection will be served by analysis of all accumulating experience. More than seven million children have been vaccinated in the United States this summer and an additional one million in Canada. Much can be learned from the results in these children. It is unlikely that the laborious pathway which has led to success in smallpox, diphtheria, tetanus and pertussis can be completely bypassed even by the use of modern calculating machines.

Such errors of judgment as have been made have occurred in all good faith, and some degree of failure should not be permitted to interfere with a cooperative effort of the public and the medical profession in a sincere attempt to solve this problem.

*Poliomyelitis Vaccine, Pediatrics, 15:788, June 1, 1955.

California MEDICAL ASSOCIATION

NOTICES & REPORTS

Executive Committee Minutes

Tentative Draft: Minutes of the 251st Meeting of the Executive Committee of the California Medical Association, Sir Francis Drake Hotel, San Francisco, July 20, 1955.

The meeting was called to order by Chairman Heron in the Tamalpais Room of the Sir Francis Drake Hotel, San Francisco, on Wednesday, July 20, 1955, at 4:00 p.m.

Roll Call:

Present were President Shipman, President-Elect Charnock, Speaker Doyle, Council Chairman Lum, Auditing Committee Chairman Heron and, ex-officio, Secretary Daniels and Editor Wilbur.

A quorum present and acting.

Present by invitation were Messrs. Hunton, Thomas, Clancy and Gillette of C.M.A. staff, legal counsel Hassard, consultant Waterson, Mr. K. L. Hamman of California Physicians' Service and Drs. A. A. Morrison, Robert C. Martin, Dan O. Kilroy and Edward C. Rosenow, Jr.

1. *Membership:*

(a) On motion duly made and seconded, members who had become delinquent and had subsequently paid their current dues were reinstated.

(b) On motion duly made and seconded in each instance, eight (8) applicants were voted Retired Membership. These were: J. Elliott Royer, Alameda-Contra Costa County; Roland Cummings, Riley Russell, Los Angeles County; Ira J. Clark, R. Manning Clarke, San Diego County; William H. Banks, George J. McChesney, San Francisco County; and Edward C. Faulkner, San Joaquin County.

(c) On motion duly made and seconded in each instance, 23 applicants were voted Associate Membership. These were: Jacob L. Bernstein, Milton G. Crane, David N. Grey, G. David Hartson, John Reynolds, Seth W. Smith, Ellen Mae Vogel, R. Stanley Woodward, Bruce V. Leamer, George B. Lewis, Los Angeles County; Harry K. Danielson, Zana Burkhart, Napa County; Bill C. Garoutte, Robert J. Roantree, David H. Wilson, San Francisco County; Thomas Doody, San Joaquin County; Willard S. Osibin, Herbert O. Swartout, San Luis Obispo County; Oliver M. Henderson, Santa Clara County; Harvey E. Robins, Santa Cruz County; Ynez C. Tyler, Solano County; and Ivan N. Radeff, Cecil P. Jones, Ventura County.

(d) On motion duly made and seconded in each instance, reductions of dues were voted for 21 applicants for reasons of postgraduate study or protracted illness.

2. *Rollen Waterson Associates:*

Mr. Waterson requested the approval of Stanford Research Institute as the body to make a pilot study of physician-patient relationships, using San Mateo County as the initial testing ground. After considerable discussion, it was agreed to defer action on this request at this time but to bring the matter before the Council after additional information has been secured.

3. *Crippled Children's Services:*

Dr. Robert C. Martin, one of the Association's appointees to a special committee to assist the State Department of Public Health evaluate the qualifications of certificated osteopathic specialists for service under the Crippled Children's Act, reported for

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the committee. The report showed that the Association representatives had been given only printed criteria and had had no opportunity to investigate the actual status of osteopathic specialty training facilities. On motion duly made and seconded, it was voted to recommend to the Council that the committee be continued and instructed to pursue its studies along practical as well as theoretical lines.

4. *Audio-Digest Foundation:*

Mr. K. L. Hamman reported that Audio-Digest Foundation had reduced its operating expenses and that for the first six months of 1955 had shown a net profit of $18,828.24. For the past few months, he said, the corporation has been operating on a profitable basis and had built up cash reserves to guarantee performance on delivery contracts paid in advance by subscribers. The rate of subscriber renewal, on the basis of very little promotion, now runs about 65 per cent.

In the expectation of potential competition to this service, Mr. Hamman expressed the belief that the corporation's profits for the next year or two should be devoted primarily to improving the quality and service of its product.

Mr. Hamman and Mr. Hassard outlined the terms of a contract just negotiated between Audio-Digest Foundation and Mr. J. L. Pettis, under the terms of which Mr. Pettis will receive an insurance contract on his life now held by the Trustees of the California Medical Association, on which Audio-Digest Foundation will pay the annual premiums. This transaction would supersede any previous agreements between Mr. Pettis and the Foundation. Approval of the transfer of the insurance policy would have to be approved by the Trustees of the California Medical Association.

On motion duly made and seconded, it was voted to approve the contract signed between Audio-Digest Foundation and Mr. J. L. Pettis and to recommend to the Trustees of the California Medical Association that they transfer the insurance policy now held on the life of Mr. Pettis to Audio-Digest Foundation, subject to payment by the latter to the Trustees of the C.M.A. the accumulated cash value on this policy.

5. *Hospital Construction Funds:*

A message from the Los Angeles County Medical Association, asking the C.M.A. to urge the State Department of Public Health to allocate federal funds for hospital construction only to new hospitals, was read and discussed. On motion duly made and seconded, it was voted to reiterate to the State Department of Public Health the policy voiced by the Association for several years of urging that funds available for hospital construction be directed at nonprofit organizations rather than governmental units.

6. *Los Angeles Medical Convention:*

A request from the Los Angeles County Medical Association for commendation of a medical convention planned in that city for early 1956 was read and discussed. On motion duly made and seconded, it was voted to refer this request to the Council.

7. *Legal Department:*

(a) Mr. Hassard reported that Mr. Pat McGee, attorney from Van Nuys, had been named to referee a disciplinary case in Ventura County; decision in this case has not yet been reached.

(b) Mr. Hassard reported that a brief had been filed in a case involving a dispensing optician who was charged with steering patients to ophthalmologists occupying rented or rent-free space in the optician's building. An appeal from a court decision holding the optician guiltless will be taken by the Board of Medical Examiners and an amicus curiae brief filed by legal counsel for the C.M.A.

8. *C.M.A. Office Arrangements:*

Mr. Hunton reported that additional office space had become available and that further space may later be available; with such added quarters, room would be available for the maintenance of some Association functions which are now carried on in outside quarters. On motion duly made and seconded, approval was voted for acquiring at this time the space now available.

9. *California Medicine:*

Dr. Wilbur reported that Dr. J. Martin Askey had found it necessary to resign as a member of the Editorial Board of CALIFORNIA MEDICINE. At Dr. Wilbur's suggestion and on motion duly made and seconded, it was voted to appoint Dr. Edward W. Boland of Los Angeles a member of the Editorial Board, to represent internal medicine and to succeed Dr. Askey.

10. *Committee Appointments:*

On motion duly made and seconded, it was voted to appoint Drs. Frederick G. Hollander of San Diego, Henry Dean Hoskins of Oakland and Donald C. Harrington of Stockton as members of the Committee on Principles of Fee Schedules, a committee of the Commission on Medical Services.

11. *Payment of Expenses:*

On motion duly made and seconded, it was voted to meet the expenses of a committee chairman who filed expense vouchers in 1955 for work undertaken in prior years.

12. *Mental Hygiene:*

(a) In response to a request from the State Director of Mental Hygiene for naming of a committee

to meet informally with him, it was regularly moved, seconded and voted to ask the Committee on State Medical Services (Drs. F. E. West, Henry A. Randel and Hollis L. Carey) to arrange such meetings, after first conferring with the chairman of the Commission on Public Policy.

(b) In regard to the Committee on Mental Health, provided for in the revised By-Laws but not yet named, it was regularly moved, seconded and voted to ask the Council Chairman to consider making this committee somewhat larger than other committees and to have its membership include physicians in specialties other than psychiatry.

(c) A report on the current status of the State Alcoholic Rehabilitation Commission was read and ordered referred to the Committee on Mental Health as soon as that body is named.

13. *Time and Place of Next Council Meeting:*

It was agreed that the next meeting of the Council would be held in Los Angeles on Sunday, August 28, 1955.

Adjournment:

There being no further business to come before it, the meeting was adjourned at 8:55 p.m.

IVAN C. HERON, M.D., *Chairman*
ALBERT C. DANIELS, M.D., *Secretary*

Standardized Insurance Forms Ready for Use

After many months of negotiations the C.M.A. Commission on Medical Services has obtained the approval of commercial insurance companies for the use of standardized insurance claims forms.

The new forms, numbered GD-1 and ID-1, are made up to cover claims for patients in group insurance contracts and those with individual insurance. Both are standardized for the use of the insurance companies and both are printed in typewriter-spaced style for ease in handling.

Use of the new forms will eliminate much of the confusion created by the present multiplicity of forms, each of which must be reviewed before it can be filled in. Where each commercial insurance company today has its own individual claims form, the new forms will supply a single style which will be recognized by the carriers.

Samples of the new forms have been sent to each member of the C.M.A., and the insurance companies will distribute copies to physicians. Current stocks of forms must be exhausted before a general distribution of the new items is made by the insurance companies but it is anticipated that within a few months the new standardized forms will be in general use.

Physicians who wish to start using these new forms at once may purchase them in pads of 100 at a cost of $1 a pad. Orders should be sent to Reynard Press, 2700 Nineteenth Street, San Francisco 10. Please remember that there are two forms, one for group coverage and one for individual insurance.

While these new forms will not completely eliminate the use of individual insurance claims forms, they will certainly be useful in the great bulk of these cases. The Health Insurance Council, which worked with the C.M.A. Commission on Medical Services in developing these forms, represents about 90 per cent of the commercial accident-health insurance business written in California and the member companies of that group have agreed to accept these uniform claims blanks in place of their own present forms. Some service plans and governmental agencies will probably continue using their own systems of claims forms.

Annual Meeting

Ambassador Hotel

LOS ANGELES

April 29 - May 2, 1956

Papers for Presentation

If you have a paper that you would like to have considered for presentation, it should be submitted *to the appropriate section secretary* (see list on this page) not later than November 19, 1955.

Scientific Exhibits

Space is available for scientific exhibits. If you would like to present an exhibit, please write immediately to the office of the California Medical Association, 450 Sutter Street, San Francisco 8, for application forms. To be given consideration by the Committee on Scientific Work, the forms, completely filled out, must be in the office of the California Medical Association not later than December 1, 1955. (No exhibit shown in 1955, and no individual who had an exhibit at the 1955 session, will be eligible until 1957.)

SCIENTIFIC PAPERS

SCIENTIFIC EXHIBITS

PLANNING MAKES PERFECT

AN EARLY START HELPS

SECRETARIES OF SCIENTIFIC SECTIONS

ALLERGY . . . . . **William J. Kerr, Jr.**
711 D Street, San Rafael

ANESTHESIOLOGY . . . . . **Robert W. Churchill**
1180 Montgomery Drive, Santa Rosa

DERMATOLOGY AND SYPHILOLOGY . . **Anker K. Jensen**
1052 West Sixth Street, Los Angeles 17

EAR, NOSE AND THROAT . . . . **E. Gordon McCoy**
490 Post Street, San Francisco 2

EYE . . . . . **Channing W. Hale**
174 Nemaha Street, Pomona

GENERAL MEDICINE . . . . . **Harold C. Sox**
300 Homer Avenue, Palo Alto

GENERAL PRACTICE . . . . . **T. Jackson Laughlin**
10910 Riverside Drive, North Hollywood

GENERAL SURGERY . . . . . **Orville F. Grimes**
U. C. Medical Center, San Francisco 22

INDUSTRIAL MEDICINE AND SURGERY . . . . . **Homer S. Elmquist**
629 So. Westlake Avenue, Los Angeles 57

OBSTETRICS AND GYNECOLOGY . . . **Ralph C. Benson**
U. C. Medical Center, San Francisco 22

ORTHOPEDICS . . . . **A. B. Sirbu (Acting Secretary)**
450 Sutter Street, San Francisco 8

PATHOLOGY AND BACTERIOLOGY . . **Justin R. Dorgeloh**
378 Thirtieth Street, Oakland 9

PEDIATRICS . . . . . **Moses Grossman**
U. C. Medical Center, San Francisco 22

PSYCHIATRY AND NEUROLOGY . **William F. Northrup, Jr.**
696 East Colorado Street, Pasadena 1

PUBLIC HEALTH . . . . . **Wilber J. Menke, Jr.**
City Hall, Pasadena 1

RADIOLOGY . . . . . **Austin R. Wilson**
540 North Central Avenue, Glendale 3

UROLOGY . . . . . **Edmund Crowley**
1930 Wilshire Boulevard, Los Angeles 57

In Memoriam

BLACKWELDER, GLENN E. Died in Paradise, July 23, 1955, aged 34, of pneumonia. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1947. Licensed in California in 1947. Doctor Blackwelder was a member of the Butte-Glenn Medical Society.

✤

BUTLER, EDMUND W. Died in Sebastopol, July 31, 1955, aged 69, of gastric hemorrhage. Graduate of the Cooper Medical College, San Francisco, 1911. Licensed in California in 1911. Doctor Butler was a member of the San Francisco Medical Society.

✤

DANIELE, JOSEPH A. Died in Crestline, July 27, 1955, aged 46. Graduate of the University of California Medical School, Berkeley-San Francisco, 1936. Licensed in California in 1936. Doctor Daniele was a member of the Los Angeles County Medical Association.

✤

DAVIS, HENRY L. Died in San Francisco, July 6, 1955, aged 65, of carcinoma of head of pancreas. Graduate of Tufts College Medical School, Boston, Massachusetts, 1914. Licensed in California in 1921. Doctor Davis was a member of the San Francisco Medical Society.

✤

FRICK, DONALD J. Died in Los Angeles, July 26, 1955, aged 81. Graduate of the University of California Medical School, Berkeley-San Francisco, 1899. Licensed in California in 1899. Doctor Frick was a retired member of the Los Angeles County Medical Association, the California Medical Association, and an associate member of the American Medical Association.

✤

HAHN, LEROY W. Died in Berkeley, July 10, 1955, aged 58, of cerebral vascular accident. Graduate of the University of California Medical School, Berkeley-San Francisco, 1928. Licensed in California in 1928. Doctor Hahn was a member of the Alameda-Contra Costa Medical Association.

✤

HAMMER, HOWARD J. Died in San Francisco, August 3, 1955, aged 46, of coronary artery disease. Graduate of Wayne University College of Medicine, Detroit, Michigan, 1935. Licensed in California in 1947. Doctor Hammer was a member of the San Francisco Medical Society.

✤

HANSON, JOEL H. Died in Redwood City, May 30, 1955, aged 62, of rheumatic heart disease. Graduate of Jefferson Medical College of Philadelphia, Pennsylvania, 1918. Licensed in California in 1919. Doctor Hanson was a member of the San Mateo County Medical Society.

✤

JACOBSON, JULIAN C. Died in Santa Cruz, July 1, 1955, aged 49, of acute coronary thrombosis. Graduate of the University of Minnesota Medical School, Minneapolis, 1935. Licensed in California in 1936. Doctor Jacobson was a member of the Santa Cruz County Medical Society.

LEAKE, NORMAN A. Died in Long Beach, July 6, 1955, aged 78. Graduate of the University of California Medical School, Berkeley-San Francisco, 1912. Licensed in California in 1912. Doctor Leake was a retired member of the Los Angeles County Medical Association, the California Medical Association, and an associate member of the American Medical Association.

✤

O'CONNOR, RODERIC P. Died in Carmel, July 6, 1955, aged 77, of myocardial infarction. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1900. Licensed in California in 1914. Doctor O'Connor was a member of the Alameda-Contra Costa Medical Association, a life member of the California Medical Association, and an associate member of the American Medical Association.

✤

ROSS, FLOYD F. Died in Berkeley, July 6, 1955, aged 54, of cardiac failure, due to occlusion left coronary artery due to arteriosclerosis. Graduate of Howard University College of Medicine, Washington, D. C., 1927. Licensed in California in 1945. Doctor Ross was a member of the Alameda-Contra Costa Medical Association.

✤

SHEPHERD, FORD. Died in Santa Cruz July 20, 1955, aged 42. Graduate of Stanford University School of Medicine, Stanford University-San Francisco, 1940. Licensed in California in 1940. Doctor Shepherd was a member of the Santa Cruz County Medical Society.

✤

SUSNOW, DAVID A. Died in San Francisco, July 20, 1955, aged 49, of coronary artery disease. Graduate of the University of California Medical School, Berkeley-San Francisco, 1930. Licensed in California in 1930. Doctor Susnow was a member of the San Francisco Medical Society.

✤

VOGEL, PHILIP. Died in San Francisco, July 15, 1955, aged 44, of Hodgkin's disease. Graduate of Rush Medical College, Chicago, Illinois, 1936. Licensed in California in 1938. Doctor Vogel was a member of the San Francisco Medical Society.

✤

WALKER, ARTHUR W. Died in Laguna Beach, July 5, 1955, aged 81. Graduate of the University of Minnesota Medical School, Minneapolis, 1909. Licensed in California in 1922. Doctor Walker was a retired member of the Riverside County Medical Association, the California Medical Association, and an associate member of the American Medical Association.

✤

YATES, JOSEPH E. Died in Sacramento, July 19, 1955, aged 74, of cerebral vascular accident. Graduate of the College of Physicians and Surgeons of San Francisco, 1904. Licensed in California in 1904. Doctor Yates was a member of the Sacramento Society for Medical Improvement, a life member of the California Medical Association, and an associate member of the American Medical Association.

WOMAN'S AUXILIARY
TO THE CALIFORNIA MEDICAL ASSOCIATION

Your Auxiliary's Role in American Medical Education Foundation

In 1951, the National Woman's Auxiliary to the A.M.A. took on the support of the American Medical Education Foundation as one of its major projects. In doing so, it embraced and endorsed the A.M.E.F. objectives: (1) to interpret the needs of medical education to the American public; (2) to encourage the advancement of medical training standards in the United States; (3) to preserve academic freedom in medical schools as well as equality of educational opportunity; (4) to foster the training of a sufficient number of competent physicians to meet the nation's health needs.

As a first step toward working with the A.M.E.F., your Auxiliary got acquainted with its background as well as its current problems.

YESTERDAY'S PROBLEMS . . . Back in 1905, the A.M.A. faced a critical situation. Medical education in the United States was lagging far behind that in many European countries. The standards of the more than 160 medical schools then functioning were haphazard. There were great differences in this regard between schools. Some of the schools were accepting entrants without complete high school educations.

How to remedy this? The first big step was taken by setting up an A.M.A. Council on Medical Education. The second big step was taken by publishing, in 1910, the results of a study made jointly by the Carnegie Foundation for the Advancement of Teaching and the A.M.A. Council. This report revolutionized American medical education. It brought about standards both for the medical schools and for the entering students which have become second to none in the world. It resulted in the weeding out of many inadequate medical schools. It gave the impetus which American medical education needed to start on its way toward the phenomenal strides it made in the decades that followed.

TODAY'S PROBLEMS . . . Today we can take stock of these strides with pride: The unparalleled advances made in American medical research; the high caliber of our practicing physicians; our American standards of health—the highest in the world.

In order to maintain our top-notch standards, we need a great deal of money. The average cost of financing the American education of a practicing physician today runs between $10,000 and $12,000. We are now graduating close to 7,000 medical students each year. Our annual "crop" of medical graduates, then, is costing between $70,000,000 and $84,000,000. Plans call for increasing the number to 7,500 in 1960. Our 79 accredited medical schools have, in many cases, woefully inadequate facilities.

Aid in the financing of our medical schools, then, is a crucial need. Your Auxiliary is proud to share in the responsibility for meeting that need through its work with the A.M.E.F.

TO INCREASE PUBLIC UNDERSTANDING . . . One of our most important functions is to acquaint not only our own members but the public with the complexities of the current situation in medical education. There are many common misconceptions. Few people realize that today we have the largest annual turn-out of graduating physicians, more approved medical schools and the largest medical enrollment that we have ever had. The vital importance of medical education to the health and welfare of the American people is another factor we must help publicize. Back of the successful control of any disease are the years of study and research which our medical schools make possible.

Because recent exigencies in some of our medical schools have called for urgent action, the A.M.A. is supporting current legislation which would also provide for federal funds to be used for physical facilities only on a "one-time" appropriation basis. Aware of the pitfalls in all-out federal subsidization, your Auxiliary is working with you for this proposed legislation.

FUND-RAISING PROJECTS . . . Of equal importance is the role your Auxiliary plays in fund-raising for the A.M.E.F. Last year, here in California, we raised nearly $5,300. The National Auxiliary contribution to the A.M.E.F. topped $80,000. Most county auxiliaries have a fund-raising project to help support the A.M.E.F. Last year, 12 of 30 county auxiliaries in California met or exceeded their A.M.E.F. quotas. Only three failed to contribute. Two counties, Alameda and Los Angeles, donated over $1,000 each, and Sonoma County gave over $500, more than $1 per member.

All sorts of methods of fund-raising are employed to get funds for A.M.E.F. Some Auxiliaries add $1 to their annual dues and earmark it for A.M.E.F.; others use white elephant sales, parties or dances to raise money. Donations "in memory" or to mark special events can be made through your Auxiliary. One notable effort was instituted by an out-of-state auxiliary which held a "dishrag party"; this set in motion the crocheting of dishrags by Auxiliary members all over the country. Their sale raised more than $15,000.

THIS YEAR'S PROGRAM . . . Your Auxiliary plans for the coming year call for the raising of funds to top those of last year. We aim for at least the $6,000 mark in A.M.E.F. donations. Furthermore, we shall continue to bend our efforts to keep ourselves—and the public—aware of the crucial needs of medical education, and of the great contribution which it makes to American life today.

NEWS & NOTES

NATIONAL • STATE • COUNTY

LOS ANGELES

Dr. Willoughby J. Rothrock has been appointed medical director of the Los Angeles City Health Department. The department's services in adult health, communicable disease control, laboratory, maternal and child health and public health nursing will be under his administrative direction. Prior to the present appointment, Doctor Rothrock was director of the tuberculosis control service and for nine months served as the Central District health officer.

* * *

Alvin G. Foord, M.D., clinical professor of pathology, University of Southern California, will lecture at the 16th annual convention of the California Association of Medical Laboratory Technicians, to be held in the Statler Hotel, Los Angeles, October 28-30. His address is titled, "The Abnormal Lymphocyte: Its Occurrence and Significance." Persons interested in attending should write Miss Barbara Holmes, 226 Fair Oaks Avenue, Apartment D, South Pasadena.

* * *

The National Multiple Sclerosis Society has provided a grant of $9,324 to Dr. Cyril B. Courville, College of Medical Evangelists professor of neurology, for **research into the destruction of nerve sheaths in the brain and spinal cord.** Dr. Courville recently announced results of earlier research which showed a relationship between lack of oxygen at birth and brain damage that results in multiple sclerosis.

SAN FRANCISCO

The **Seventh Annual Scientific Assembly of the California Academy of General Practice** will be held at the Sheraton-Palace Hotel in San Francisco on October 9-12, 1955. A total of twenty-two papers will be presented covering medical, obstetrical and surgical subjects.

Seven of the speakers on the program are from out-of-state. They are Joe Vincent Meigs, M.D., Boston; Edward H. Rynearson, M.D., professor of medicine at the Mayo Foundation; Perry S. MacNeal, M.D., Philadelphia; Charles W. McLaughlin, Jr., M.D., Nebraska Medical School; Edward S. Judd, Jr., M.D., the Mayo Foundation; Goodrich C. Schauffler, M.D., lecturer on gynecology from the University of Oregon; and William H. Gordon, M.D., Lubbock, Texas.

Physicians who are not members of the American Academy of General Practice may attend this meeting upon payment of a $5 registration fee. Further information may be obtained from Dr. John G. Walsh, president, California Academy of General Practice, 461 Market Street, San Francisco.

* * *

Newly elected officers of the **Allergy Foundation of Northern California, Inc.,** are: Chairman of the board of governors, Dr. M. Coleman Harris, San Francisco; vice-chairman, Dr. Grace Talbott, San Francisco; secretary-treasurer, Dr. Albert Rowe, Jr., Oakland.

Program for the **26th Annual Postgraduate Symposium of the San Francisco Heart Association,** which is to be held October 5-7 in the St. Francis Hotel, San Francisco, follows:

WEDNESDAY MORNING, OCTOBER 5, 1955
9:00 a.m.-12:00 m.

Electrocardiography and Vectorcardiography

Presiding: David A. Rytand, M.D.

9:00-9:45 a.m.—The Nature of ST and T Wave Changes—Myron Prinzmetal, M.D.

9:45-10:30 a.m.—Value of Vector Methods and Vectorcardiograms in Clinical Cardiography — Franklin D. Johnston, M.D.

10:30-10:45 a.m.—Recess. Time to visit the exhibits.

10:45-12:00 m.—Diagnostic Implications of Electrocardiography and Vectorcardiography—Panel.

Moderator: David A. Rytand, M.D.

Participants: Franklin D. Johnston, M.D., Myron Prinzmetal, M.D., Arthur Selzer, M.D., Maurice Sokolow, M.D.

WEDNESDAY AFTERNOON, OCTOBER 5, 1955
1:30 p.m.-5:00 p.m.

Session on Congenital Heart Disease

Presiding: Joseph Davis, M.D.
President, Northern California Pediatric Society

1:30-2:15 p.m.—Basic Anatomic Abnormalities in Congenital Malformations of the Heart—Edith L. Potter, M.D.

2:15-3:00 p.m.—Some Observations on the Vascular Pedicle—D. Evan Bedford, M.D.

3:00-3:15 p.m.—Recess. The exhibits will interest you.

3:15-4:00 p.m.—New Techniques for Laboratory Diagnosis of Congenital Heart Disease—Elliot V. Newman, M.D.

4:00-5:00 p.m.—Treatment of Congenital Heart Disease—Panel.

Moderator: Mary B. Olney, M.D.

Participants: D. Evan Bedford, M.D., Frank Gerbode, M.D., Sanford E. Leeds, M.D., Elliot V. Newman, M.D., Edith L. Potter, M.D., Helen B. Pryor, M.D.

THURSDAY MORNING, OCTOBER 6, 1955
9:00 a.m.-12:00 m.

Pathology and Diagnosis

Presiding: Hilliard J. Katz, M.D.

9:00-9:15 a.m. — President's Address: The Challenge of Clinical Teaching of Cardiology—Hilliard J. Katz, M.D.

9:15-10:00 a.m.—Abnormalities of the Aortic Arch—Edith L. Potter, M.D.

10:00-10:50 a.m.—Clinical Pathology of the Pulmonary Artery—D. Evan Bedford, M.D.

10:50-11:10 a.m.—Recess. Time to visit the exhibits.

11:10-12:00 m.—Some Remarks About Stethoscopes and Heart Murmurs—Franklin D. Johnston, M.D.

THURSDAY AFTERNOON, OCTOBER 6, 1955
1:30 p.m.-5:00 p.m.

Session on Coronary Artery Disease

Presiding: Kenelm W. Benson, M.D.

1:30-2:15 p.m.—Evolution of Our Conceptions of Angina Pectoris and Coronary Disease—D. Evan Bedford, M.D.

2:15-3:00 p.m.—Clinical Applications of Intramural Electrocardiography—Myron Prinzmetal, M.D.

3:00-3:15 p.m.—Recess. Don't forget the exhibits.

3:15-4:00 p.m.—Important Points in the Diagnosis and Management of Patients with Coronary Artery Disease —Franklin D. Johnston, M.D.

4:00-5:00 p.m.—Treatment and Management of Arteriosclerosis and Coronary Artery Disease—Panel.

Moderator: John J. Sampson, M.D.

Participants: D. Evan Bedford, M.D., I. Lyon Chaikoff, M.D., Franklin D. Johnston, M.D., Myron Prinzmetal, M.D., Robert L. Smith, Jr., M.D.

THURSDAY EVENING, OCTOBER 6, 1955

Dinner Meeting

7:00 p.m.—Mural Room, St. Francis Hotel

Presiding: Hilliard J. Katz, M.D., President

New Lamps for Old in Cardiology—D. Evan Bedford M.D.

(The Mural Room will be open at 6:00 p.m. for cocktails)

FRIDAY MORNING, OCTOBER 7, 1955
9:00 a.m.-12:00 m.

Treatment of Heart Disease

Presiding: Mast Wolfson, M.D.

9:00-9:45 a.m.—Principles and Complications of Diuretic Therapy—Elliot V. Newman, M.D.

9:45-10:30 a.m.—Indications for Therapeutic Myxedema—D. Evan Bedford, M.D.

10:30-10:45 a.m.—Recess. Last call to see the exhibits.

10:45-12:00 m.—Panel Discussion.

Moderator: Francis L. Chamberlain, M.D.

Participants: D. Evan Bedford, M.D., Isidore S. Edelman, M.D., John A. Luetscher, Jr., M.D., Elliot V. Newman, M.D., Myron Prinzmetal, M.D.

FRIDAY AFTERNOON, OCTOBER 7, 1955
1:30 p.m.-5:00 p.m.

Clinical Session

Colonial Ballroom

Presiding: Arthur L. Bloomfield, M.D.
William J. Kerr, M.D.

Participants: D. Evan Bedford, M.D., Franklin D. Johnston, M.D., Elliot V. Newman, M.D., Edith L. Potter, M.D., Myron Prinzmetal, M.D. Patients with various types of heart disease will be presented by local physicians and discussed by guest speakers.

GENERAL

The annual meeting of the **Western Society for the Study of Sterility** will be held in Palm Springs, California, November 4-6. Attendance is open to all physicians and to persons in allied fields. Dr. Earle Marsh, San Francisco, is program chairman. Dr. Alan Guttmacher of New York will be guest speaker. Advance registration (Fee $10 for nonmembers) may be made by writing Dr. Edward T. Tyler, secretary-treasurer, 10911 Weyburn Avenue, Los Angeles 24.

* * *

The annual convention of the American College of Gastroenterology will be held at the Shoreland in Chicago, October 24-26.

The **annual course in postgraduate gastroenterology,** under the personal direction of Dr. Owen H. Wagensteen of Minneapolis and Dr. I. Snapper of Brooklyn, will be given on October 27-29 at the Shoreland.

The **scientific sessions** on October 24-26 are open to all physicians without charge. The postgraduate course will only be open to those who have matriculated in advance. Copies of the program and further information concerning the postgraduate course may be obtained by writing to: American College of Gastroenterology, 33 West 60th Street, New York 23, N. Y.

* * *

In a recent letter to Dr. Sidney J. Shipman, president of the California Medical Association, Dr. Howard A. Rusk, chairman of the **American-Korean Foundation,** said: "As we enter the third year of the Korean Medical Education program which has been conducted by the American-Korean Foundation in cooperation with the Office of the Surgeon General to gather **medical books and journals** for Korea, I would like to express our deep gratitude to you for the contribution you have made to the success of this project.

"Through the generous cooperation of physicians, hospitals, state and medical societies and pharmaceutical houses all over the country 122,697 pounds of books and journals have been shipped to Korea since the summer of 1953. Korean institutions who have shared in this valuable gift include Seoul National University, Severance Medical College, Ewha University, Taegu Medical College, Kwangju Medical College and the School of Public Health.

"Anyone having surplus medical literature they desire to donate to the American-Korean Foundation may send it to the Medical Supply Officer, Sharpe General Depot, Tracy Annex, Lathrop, California. The need is still great for all kinds of medical literature. The gift should be plainly marked as a donation to American-Korean Foundation."

* * *

The **Academy of Psychosomatic Medicine** will hold its second annual meeting on October 6-8 at the Plaza Hotel in New York City. The subject of this year's scientific program is "The Psychosomatic Aspects of Drug Administration." There is no registration fee.

* * *

The American Goiter Association again has announced its **annual contest for the Van Meter Prize Award** of $300 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the Association which will be held at the Drake Hotel, Chicago, May 3, 4 and 5, 1956, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed 3,000 words in length and must be presented in English. Duplicate typewritten copies, double spaced should be sent to the secretary, Dr. John C. McClintock, 149½ Washington Avenue, Albany, New York, not later than January 1, 1956.

POSTGRADUATE EDUCATION NOTICES

THIS BULLETIN of the dates of postgraduate education assemblies and the meetings of various medical organizations in California is supplied by the Committee on Postgraduate Activities of the California Medical Association. In order that they may be listed here, please send communications relating to your future medical or surgical programs to: Mrs. Margaret H. Griffith, Assistant Director, Postgraduate Activities, California Medical Association, 417 South Hill Street, Los Angeles 13.

UNIVERSITY OF CALIFORNIA AT LOS ANGELES

Surgical Anatomy, Tuesday evenings, September 20 to November 22, 1955.

Advanced Treatment of Emotional Problems, Thursday evenings, September 22 to December 15, 1955.

Annual Medical Lecture Series, Monday evenings, October 3 to December 19, 1955.

Application of Principles of Industrial Medicine to Private Practice, Wednesday evenings, October 19 to December 14, 1955.

Aviation Medicine, Tuesday, Wednesday and Thursday, October 25, 26 and 27, 1955.

Pediatrics, Thursday, Friday and Saturday, October 27, 28 and 29, 1955.

Three Symposia: RIVERSIDE, Wednesdays, September 21, 28 and October 5, 1955—(a) What's New in Medicine; (b) Fevers of Unexplained Origin; (c) Obstetrics.

Three Symposia: SAN DIEGO, Wednesdays, October 26, November 2 and 9, 1955—(a) Radioisotopes; (b) Surgery of the Hand; (c) Burns, one-half day; Repair of Superficial Wounds, one-half day.

Contact: Thomas H. Sternberg, M.D., Assistant Dean for Postgraduate Medical Education, U.C.L.A., Los Angeles 24.

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

In San Francisco:

Conference on Applied Therapeutics—October 17, 18 and 19.

Conference on Gynecology and Obstetrics—October 20 and October 21.

Ophthalmological Conference—December 5 to December 7.

Postgraduate Surgical Programs in cooperation with Surgical Service of Fort Miley VA Hospital and sponsored by the San Francisco Chapter, American Academy of General Practice. Fort Miley VA Hospital Auditorium, 42nd Avenue and Clement Street, San Francisco. Tuesday evenings, September 20-November 8. Programs available at California Academy of General Practice, 461 Market Street, San Francisco.

In East Oakland:

Medicine for General Practitioners—Tuesday evenings, September 20 to December 6.

In Berkeley:

Postgraduate Institute—Wednesday evenings, Herrick Memorial Hospital, October 19 through November 23.

In San Mateo:

Evening Lectures in Medicine—Thursday evenings, September 22 to December 15.

Contact: Seymour M. Farber, M.D., Head, Postgraduate Instruction, Office of Medical Extension, University of California Medical Center, San Francisco 22.

UNIVERSITY OF SOUTHERN CALIFORNIA, LOS ANGELES

In Ventura:

No. 843: Recent Advances in Diagnosis and Treatment. In cooperation with the Ventura County Medical Association. Six weekly lectures beginning September 29-November 3, 1955.

In Los Angeles:

No. 873: Cardiac Resuscitation. Sponsored by the Los Angeles County Heart Association. Each Wednesday throughout the year, U.S.C. Medical Research Building. $30 per session.

Contact: Phil R. Manning M.D., Director of Medical Extension Education, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 33.

STANFORD UNIVERSITY

Important Recent Advances in Treatment in General Practice. September 12, 13, 14, 1955. 9 a.m. to 4:30 p.m. Fee, $75.00.

Recent Advances in General Surgery and Surgical Anatomy. September 12 through 16, 1955. 8:30 a.m. to 4:30 p.m. Fee, $125.00.

Contact: Office of the Dean, Stanford University School of Medicine, 2398 Sacramento St., San Francisco 15.

COLLEGE OF MEDICAL EVANGELISTS

Announces graduate courses:

General Surgery and Surgical Specialties—October 2 to June 8, 1956.

Internal Medicine—October 2 to June 8, 1956.

Otolaryngology—October 2 to June 8, 1956.

Contact: Chairman, Section on Graduate and Postgraduate Medicine, College of Medical Evangelists, 1720 Brooklyn Ave., Los Angeles 33.

CALIFORNIA MEDICAL ASSOCIATION, POSTGRADUATE ACTIVITIES CIRCUIT COURSES

NORTH COAST CIRCUIT in association with Stanford University School of Medicine:

Eureka—Monday, October 17, 24, 31, November 7.
Ukiah—Tuesday, October 18, 25, November 1, 8.
Woodland—Wednesday, October 19, 26, November 2, 9.
Napa—Thursday, October 20, 27, November 3, 10.

SACRAMENTO VALLEY CIRCUIT in association with University of California School of Medicine, San Francisco:

Dunsmuir—Monday, October 17, 24, 31, November 7.
Chico—Tuesday, October 18, 25, November 1, 8.
Marysville—Wednesday, October 19, 26, November 2, 9.
Auburn—Thursday, October 20, 27, November 3, 10.

POSTGRADUATE INSTITUTES

SOUTHERN COUNTIES in association with the University of Southern California School of Medicine, January 19-20, 1956, at Laguna Beach.

WEST COAST COUNTIES in association with College of Medical Evangelists, March 1-2, 1956, in Carmel.

NORTH COAST COUNTIES in association with University of California School of Medicine, San Francisco, April 5-6, 1956, in Santa Rosa.

SAN JOAQUIN VALLEY COUNTIES in association with the University of California School of Medicine, Los Angeles, mid-April, 1956, in Fresno.

SACRAMENTO VALLEY COUNTIES in association with Stanford University School of Medicine, June 21, 22, 1956, at Lake Tahoe.

Contact: C. A. Broaddus, M.D., Director of Postgraduate Activities, P.O. Box A-1, Carmel, California, or Mrs. Margaret H. Griffith, Assistant Director, California Medical Association, 417 So. Hill St., Los Angeles 13.

Medical Dates Bulletin

SEPTEMBER MEETINGS

SAINT JOHN'S HOSPITAL announces its Seventh Annual Postgraduate Assembly, September 12, 13 and 14, Elk's Club, Santa Monica. All physicians invited to attend. Registration fee, $10.00.

Contact: John C. Eagan, M.D., Director, Postgraduate Assembly, St. John's Hospital, 22nd Street at Santa Monica Blvd., Santa Monica.

SAN DIEGO COUNTY HOSPITAL NINTH POSTGRADUATE ASSEMBLY, September 21 and 22.

Contact: Howard B. Kirtland, Jr., M.D., 3505 Fourth Ave., San Diego 3.

CANCER CONFERENCE, St. Francis Hotel, San Francisco, 2 p.m., September 30, American Cancer Society, California Division.

Contact: Walter E. Batchelder, M.D., 467 O'Farrell St., San Francisco 2.

OCTOBER MEETINGS

CALIFORNIA SOCIETY OF INTERNAL MEDICINE meeting at Biltmore Hotel, Santa Barbara, October 1, 1955.

Contact: Mildred D. Coleman, secretary, 384 Post St., San Francisco.

SAN FRANCISCO HEART ASSOCIATION, Twenty-sixth Annual Postgraduate Symposium on Heart Disease, at St. Francis Hotel, San Francisco. October 5, 6, 7, 1955.
Contact: 604 Mission St., San Francisco 5.

SAN DIEGO COUNTY HEART ASSOCIATION Annual Symposium on Heart Disease, U. S. Naval Hospital, Auditorium, Balboa Park, San Diego, October 11.
Contact: H. Jack Hardy, executive secretary, 1651 Fourth Avenue, San Diego.

LOS ANGELES COUNTY HEART ASSOCIATION 25th Annual Symposium on Cardiovascular Diseases, Wilshire-Ebell Theater, Los Angeles, October 12 and 13.
Contact: Los Angeles County Heart Association, 316 So. Bonnie Brae Street, Los Angeles.

The 1955 Scientific Assembly of the CALIFORNIA ACADEMY OF GENERAL PRACTICE will be held in San Francisco, at the Sheraton-Palace Hotel, October 9-12, 1955.
Contact: William W. Rogers, executive secretary, 461 Market St., San Francisco.

STATE BOARD OF MEDICAL EXAMINERS Written Examination, Sacramento, October 17-20.†

Mid-October—AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY Examinations, San Francisco.
Contact: David A. Boyd, M.D., Secretary, 102-110 Second Avenue, S.W., Rochester, Minn.

NOVEMBER MEETINGS

AMERICAN MEDICAL ASSOCIATION Clinical Session, 1955, in Boston, November 29 to December 2, 1955.

STATE BOARD OF MEDICAL EXAMINERS Oral Examination for Reciprocity Applications, San Francisco, November 12.†

STATE BOARD OF MEDICAL EXAMINERS Oral and Clinical Examinations for Foreign Medical School Graduates, San Francisco, November 13.†

DECEMBER MEETINGS

MEDICAL ALUMNI COMMITTEE OF CHILDREN'S HOSPITAL, San Francisco, December 2, 9:30 a.m.* Prenatal Problems, Departments of Obstetrics, Anesthesia, Pediatrics and Public Health, participating.

AMERICAN COLLEGE OF CHEST PHYSICIANS, Ambassador Hotel, Los Angeles, December 5-10. Los Angeles Postgraduate Course on Diseases of the Chest.
Contact: Alfred Goldman, M.D., Chairman, 416 North Bedford Drive, Beverly Hills.

JANUARY MEETINGS

LOS ANGELES MIDWINTER MEDICAL CONVENTION, January 3, 4, 5, 1956, Biltmore Hotel, Los Angeles. An 85th anniversary, sponsored by Los Angeles County Medical Association.
Contact: Jerry L. Pettis, Public Relations Counsel, Los Angeles County Medical Association, 1925 Wilshire Blvd., Los Angeles 57. Telephone DUnkirk 5-1581.

MEDICAL ALUMNI COMMITTEE OF CHILDREN'S HOSPITAL, San Francisco, January 14, 1956.* Pediatric Surgery, with special emphasis on diagnosis, referral, preparation, pre- and postoperative care.

SPRING MEETINGS

MEDICAL ALUMNI COMMITTEE OF CHILDREN'S HOSPITAL, San Francisco, March 17, 1956.* Morning: Dermatology. Afternoon: Nutritional problems peculiar to modern pediatrics.

MEDICAL ALUMNI COMMITTEE OF CHILDREN'S HOSPITAL, San Francisco, April 14, 1956.* Behavior Problems and Childhood Psychiatry.

CALIFORNIA MEDICAL ASSOCIATION ANNUAL MEETING, Ambassador Hotel, Los Angeles, April 29-May 3, 1956.
Contact: John Hunton, Executive Secretary, 450 Sutter St., San Francisco 8, or Ed Clancy, Director of Public Relations, 417 S. Hill St., Los Angeles 13.

AMERICAN COLLEGE OF PHYSICIANS 37TH ANNUAL SESSION, Los Angeles, April 16-20, 1956.
Contact: George C. Griffith, M.D., General Chairman, Box 25, 1200 N. State St., Los Angeles 33.

**For registration or information, contact:* Gertrude Jones, M.D., Children's Hospital, San Francisco.

†*For information contact:* Louis E. Jones, M.D., secretary-treasurer, California State Board of Medical Examiners, Room 536, 1020 N Street, Sacramento. (Note: Applications must be on file at least two weeks before examination dates.)

THE PHYSICIAN'S *Bookshelf*

PERINATAL MORTALITY IN NEW YORK CITY—Responsible Factors. Schuyler G. Kohl, M.S., M.D., Dr. P.H., Commonwealth Fund, Harvard University Press, Cambridge, Mass., 1955. 112 pages, $2.50.

This small book represents a painstaking analysis of 955 stillbirths and neonatal deaths occurring in New York City in 1950. It is published under the auspices of the New York Academy of Medicine and represents primarily the work of its subcommittee on Neonatal Mortality. The statistical analyses have been carried out in the Columbia School of Public Health. The purpose of the study is not to duplicate information available from vital statistics records, but is "to concentrate on preventability, responsibility, cause of death, and related clinical data." This the book does well. Attention is given to such factors as the following in their relation to perinatal deaths: type of obstetrical care, age and parity of the mother, obstetric complications, analgesia and anesthesia, method of delivery, and time of death. A significant chapter is devoted to causes of death and their agreement on pathologic, clinical, and recorded death certificate bases. The final chapter summarizes the findings of the study, set forth in twenty-four points; in addition the author offers a number of suggestions of value to those undertaking future investigations of a similar type. This book may be recommended to obstetricians, pediatricians, and public health workers concerned especially with the statistical approach to problems of perinatal mortality. Organizations concerned with fetal and neonatal deaths will find it a useful reference.

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BONE AND JOINT X-RAY DIAGNOSIS. Max Ritvo, M.D., Assistant Clinical Professor of Radiology, Harvard Medical School. Lea & Febiger, Philadelphia, 1955. 752 pages, 568 illustrations, $20.00.

This comprehensive textbook is divided into ten chapters of widely varying lengths. The opening chapter deals with general considerations of radiology and osteology. There are chapters on hereditary and congenital disorders of the skeleton, traumatic lesions, infections, endocrine and metabolic disturbances, and bone changes due to chemical and physical agents. The next chapter deals with diseases of the joints and periarticular tissues. The last three chapters deal with bone tumors, diseases of the spinal canal and soft tissue roentgenography of various portions of the body.

In general, there is adequate discussion of the clinical, pathological and roentgenological manifestations of bone disorders; there are occasional references to treatment and there are good sections on differential diagnosis. The references to the literature are rather sparse, and the number of illustrations somewhat modest for a seven hundred-fifty page book (the illustrations number 398). However, the latter are in positive form and are of very good quality. The book, therefore, would appear to be primarily for students, and one to be used in conjunction with a good roentgen teaching file. Most of the material comes from the Boston City Hospital at which the author is Director of the Department of Radiology.

CHRISTOPHER'S MINOR SURGERY — 7th ed. Alton Ochsner, M.D., F.A.C.S., William Henderson Professor of Surgery and Chairman of the Department of Surgery, Tulane University School of Medicine; and Michael E. DeBakey, M.D., F.A.C.S., Professor of Surgery and Chairman of the Department of Surgery, Baylor University College of Medicine, W. B. Saunders Company, Philadelphia, 1955. 547 pages, 251 illustrations, $9.00.

Christopher's *Minor Surgery* has been for many years one of the outstanding texts on minor surgery. It has not been revised for seven years, however, and the present revision, which constitutes the seventh edition, has been admirably accomplished by Ochsner and DeBakey. These authors have changed the format of the book entirely, and since the many contributors to this new volume were all at one time or another closely associated with Ochsner and DeBakey the book maintains a uniformity of presentation despite its multiple authorship. It is clearly and concisely written. The subject material covered is well arranged and the illustrations are reasonably adequate. Condensation from previous volumes has been accomplished by avoiding the innumerable references and quotations from countless authors which heavily burdened the previous editions. One good method of treatment is given for each condition and the reader is no longer left to choose from a variety of different methods of managing minor surgical lesions.

The term "minor surgery" has never been adequately or clearly defined, and the book suffers in scope since it is limited to a discussion of conditions in which there is little or no threat to life. Many readers will be disappointed in the failure to cover many subjects which they would hope to have discussed to make the book more useful in everyday practice of surgery. Insufficient detail is also given in many of the discussions to permit pertinent judgments in the course of treatment of many conditions discussed. On the whole, however, the present edition is superior to any of the earlier ones, and it is a good book on "Minor Surgery."

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HYPERTENSION—Humoral and Neurogenic Factors—Ciba Foundation Symposium. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Margaret P. Cameron, M.A., A.B.I.S. Little, Brown and Company, Boston, 1954. 294 pages, 73 illustrations, $6.75.

This is the record of some twenty papers and the discussions evoked by them at a meeting in 1953 of 33 students of hypertension gathered in London from North and South America, England, Spain, Sweden, etc. For the most part, the material is more academic than practical (neural and humoral control of blood vessels, renin, 5-hydroxytryptamine, catechol amines). A number of chapters, such as those on hypertensive disease without hypertension, role of the kidney in hypertension, the relationships between water, electrolytes, the adrenals and arterial pressure, and ganglion blocking agents, should be of wider interest. The provocative discussions are valuable. The work contains adequate illustrations and indexes; it is well published and represents an excellent review of the current state of advances toward the understanding of arterial hypertension.

SURVEY OF CLINICAL PEDIATRICS—Second Edition. Lawrence B. Slobody, M.D., Professor of Pediatrics, New York Medical College, The Blakiston Division, McGraw-Hill Book Company, Inc., New York, 1955. 502 pages, $9.50.

The title of the book describes it. It is a survey of Clinical Pediatrics. This is a good survey. Knowledge and facts concerning growth, development and the pathological conditions seen in children are presented in outline form with brevity of words, but each sentence is full of knowledge and known facts. Each subject is captioned in large bold type. The numerous tables stand out sharply in the text. Each condition described outlines the essential features of the disease or pathological condition, the germane laboratory procedures are listed and essential treatment described, with dosage and procedures listed in detail. At the end of each chapter there is a list of "review questions" which challenges the reader as to his grasp of the chapter. The index covers 51 pages. There are three pages of suggested collateral and reference reading. The preface states, "The survey is not intended to replace the excellent text books now available. It is designed to help the student and practitioner focus on the highlights and relationships of pediatrics." The reviewer feels this has been done. Some information is so new that even the Salk Vaccine is mentioned. The book could even serve the well established pediatrician as a quick and easy review of conditions and diseases affecting the growing child.

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CIBA COLLECTION OF MEDICAL ILLUSTRATIONS—Volume 2—Reproductive System. Prepared by Frank H. Netter, M.D., and Edited by Ernst Oppenheimer, M.D. Commissioned and published by CIBA Pharmaceutical Products, Inc., Summit, New Jersey, 1954. 286 pages, $13.00.

In his foreword to this atlas, John Rock aptly describes it as an exceedingly compact and inclusive postgraduate course in both male and female reproductive anatomy, physiology and pathology. To those familiar with the first volume of Ciba Medical Illustrations (on the nervous system), suffice it to say that the second is a similar but more pretentious effort, comprising 233 plates with accompanying descriptive text printed in very small type. Many of Frank Netter's illustrations will be familiar to physicians who have had time to look at the various issues of "Ciba Clinical Symposia," as well as special folders and brochures distributed by this pharmaceutical concern over the last dozen years, because 144 of the plates were published previously in these media. In addition to a preface describing briefly some of the problems of putting such an atlas together, Ernst Oppenheimer has provided an impressive sketch which tells something of the enormous amount of study Doctor Netter devotes to the subject depicted in each of his paintings. Finally, the artist himself has provided a short historical resumé of the work of artist-illustrators in medicine, as well as interesting comments about his collaborators who provided the textual material.

The volume is divided conveniently into fourteen sections, the first five of which deal with normal anatomy and diseases of the male genital tract. Similar coverage for the female organs is provided in the next six sections, and the remaining three portions are devoted respectively to pregnancy and its disorders, the mammary gland, and intersexes. Netter's paintings of gross anatomical and pathological material are superb, but many of the reproductions of photomicrographs seem oversimplified and perhaps in many instances the actual photographs might have served better.

The book is recommended to those who need a fairly rapid and pleasantly colorful review of disorders of the reproductive systems. Teachers will find that many of the plates, or portions of them, can be reproduced nicely on color film and used as transparencies for lantern slides, a practice which one presumes to be in keeping with the avowed purpose of the authors.

PSYCHOPHYSIOLOGIC MEDICINE. Eugene Ziskind, M.D., Clinical Professor of Psychiatry, University of Southern California School of Medicine. Lea & Febiger, Philadelphia, 1954. 370 pages, $7.00.

In recent years there have been many volumes popularizing the field of psychosomatic medicine. This one, by a practicing psychiatrist who has been working for many years as a psychiatrist in a general hospital and clinic, may prove to be a real help to physicians interested in the psychological aspects of medicine. The author divides his presentations into three sections—the first concerned with a generally comprehensive description of the problems of psychophysiologic medicine and related psychopathological aspects of such problems; the second with techniques and methodology, including diagnosis and psychotherapy; and the third, entitled "Toward Broader Visions," describes child-parent relationships, the social factors of psychopathology, psychiatric emergencies in medical practice, and a description of the various schools of psychiatric thought, including those of Freud, Adler, Jung, Rank, the cultural psychoanalysts, and Meyer, the psychobiologist. The presentation is simple and lucid. Clinical examples are sprinkled throughout the text in order to emphasize specific points and are quite appropriately chosen, and no attempt is made to minimize the difficulties in inherent psychotherapeutic procedures. The author's basic philosophy is stated as follows: "I stress what is common to most psychiatric thinking, namely, that the needs of human beings, when frustrated, result in personality conflicts; that the process of social adaptation is universal, but often unsuccessful; that early life conflicts endure; that persistent conflicts may crystallize into character patterns; that unresolved conflicts may be transmitted into symptoms of organic illness through the autonomic nervous system. These do not explain all psychopathology yet they suffice as a set of working premises."

All in all, this book may be highly recommended to practicing physicians and students.

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SYNOPSIS OF MEDICINE—Tenth Edition. Sir Henry Letherby Tidy, K.B.E., M.A., M.D., B.Ch.(Oxon), F.R.C.P. (Lond.), Extra Physician to Her Majesty the Queen. The Williams and Wilkins Company, Baltimore, 1954. 1253 pages, $7.50.

It is obvious that this short synopsis of medicine has filled a need because of its many editions since 1920, of which the present one is the tenth. The material in general is well organized and easily available by an excellent index. The basic principles are clearly stated but the discussion is, to the reviewer's mind, wholly inadequate. This may, of course, be the result of the limited space available because of the nature of the book. Nevertheless, one often finds inadequate discussions, as for example, the fact that Coronary Heart Disease is covered in five and one-half short pages and Essential Hypertension in two pages. Treatment is particularly inadequately covered. Newer methods of study have been incorporated in the new edition, although one still finds discussions, as in the section on Coronary Heart Disease mentioned above, with respect to Lead IV rather than discussing the precordial leads.

The section on Infectious Diseases is among the best although again treatment is given inadequate attention. The space devoted to Infectious Diseases is much more adequate than for other aspects of medicine, which may account for the excellence of this particular section. For example, the discussion on Lobar Pneumonia covers thirteen pages.

For those who like their medicine in capsule form and who are able to gain what they want from terse statements, this book will be useful.

THE PHYSIOLOGICAL BASIS OF MEDICAL PRACTICE—A Text in Applied Physiology. Charles Herbert Best, C.B.E., M.A., M.D., D.Sc.(Lond.), F.R.S., F.R.C.P. (Canada), Professor and Head of Department of Physiology, Director of the Bantin-Best Department of Medical Research, University of Toronto; and Norman Burke Taylor, V.D., M.D., F.R.S.(Canada), F.R.C.S.(Edin.), F.R.C.P. (Canada), M.R.C.S.(Eng.), L.R.C.P.(Lond.), Professor of History of Medicine and Medical Literature, University of Western Ontario. The Williams and Wilkins Company, Baltimore, 1955. 1357 pages, $12.00.

This time-tested and standard text on applied physiology is again recommended as a link between basic medical science and the practice of medicine. It contains a great mass of information readily available for the student of clinical medicine, the intern and the practitioner with a scientific bent.

Despite the fact that the present edition has had considerable change, the reviewer feels that the revision is still patchy and not extensive enough. The section on the endocrine glands may be cited as an example of too little alteration in the text and particularly in the illustrations. One sees the same pictures, including the same old outworn extreme abnormalities, often badly reproduced, that were present in the first edition of 1937.

In view of the value and the stature of this book we hope that the next edition will show even more improvement.

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MYOCARDIAL INFARCTION—Its Clinical Manifestations and Treatment with Anticoagulants—A Study of 1,031 Cases. Irving S. Wright, M.D., Charles D. Marple, M.D., and Dorothy Fahs Beck, Ph.D., Report of the Committee on Anticoagulants, American Heart Association. Published for the American Heart Association by Grune & Stratton, New York, 1954. 656 pages, $8.50.

This massive monograph presents a final report which demonstrates again that, during a cooperative study under the direction of the Committee on Anticoagulants, certain patients with myocardial infarction who received anticoagulants had a lower mortality rate than others who were not so treated. Extensive documentation gives evidence which convinces the authors that this beneficial effect may be attributed to the use of anticoagulants rather than to other factors in the management or selection of patients. Inasmuch as such factors bear on prognosis after myocardial infarction, the validity of the authors' conclusions depends upon their demonstration of random selection of patients during this clinical trial. Unusually detailed analyses are presented to establish this point. In the end, the reader must judge for himself whether the analyses and correction factors for certain differences between control and treated groups are valid. The committee is to be congratulated for completing its monumental task.

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MANUAL OF HAND INJURIES. H. Minor Nichols, M.D., Clinical Instructor in Surgery, University of Oregon Medical School. The Year Book Publishers, Inc., 200 East Illinois, Chicago, 1955. 352 pages, $9.50.

This manual fulfills the need of a less ponderous text encompassing most of the commonplace injuries of the hand. Thus, it has value to general practitioners, surgeons, and students. The book has been carefully done and covers most salient points in the primary care of injury. It is garnished by a chapter on anatomy and one on general technique, including preoperative and postoperative care. At the end of the book, a chapter on secondary tendon repair and another on elective and reconstructive procedures serve as an introduction to the more complicated and extensive problems in this field.

Dr. Nichols, known personally by the reviewer, has had a wealth of experience and takes a practical approach to the problem of rehabilitating the injured hand.

RECENT ADVANCES IN MEDICINE AND SURGERY—Vols. I and II—(19-30 April 1954). Based on Professional Medical Experiences in Japan and Korea 1950-1953. Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D. C., Medical Science Publication No. 4. Superintendent of Documents, U. S. Government Printing Office, Washington 25, D.C. $1.75.

These two volumes represent complete notes of a course entitled "Recent Advances in Medicine and Surgery," conducted by the Army Medical Service School, 19 to 30 April 1954. The faculty was selected from surgeons who actually performed large numbers of operations under battlefield conditions, individuals concerned with public health and preventive medicine responsibilities, and internists concerned with large numbers of cases of hepatitis, malaria and other diseases.

The authors emphasized the difficulties they had and the mistakes they made as they gained experience in evacuation, management of early wounds and personnel problems. Also they were confronted with a new disease, epidemic hemorrhagic fever, in enormous numbers of cases, without having had any practical experience in its management. A novel approach to the solving of this latter problem, as well as many other medical field problems, was enthusiastically and effectively managed by moving experts in their respective fields from Walter Reed Army Medical Center, plus groups of civilian medical specialists, to the field treatment centers in Korea.

These two volumes would be of value to any practicing physician because they are authoritative and cover many of the problems doctors would be confronted with in case of a national disaster.

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A TEXTBOOK OF NEUROLOGY. H. Houston Merritt, M.D., Professor of Neurology, Columbia University. Lea & Febiger, Philadelphia, 1955. 746 pages, 181 illustrations and 128 tables, $12.50.

This is a new textbook of neurology by an author who belongs to the relatively younger generation of specialists in this field. In order to justify its existence it must have virtues not possessed by the fairly numerous texts which have undergone the refinement of passing through a number of editions. These, in the opinion of the reviewer, are present. Primarily, the whole approach to the subject is modern, and does not show the piecemeal revision that is inherent in an older book periodically brought up to date. The various diseases of the nervous system are arranged as much as possible according to etiology. This is an advantage to the student, and coupled with the excellent index provided is in no way disadvantageous to the physician using the book as a reference work. The subject is treated exclusively from the clinical standpoint, anatomical data and the technique of examination being introduced only where necessary to clarify a particular point. In all, this is a useful addition to the list of neurological texts, and can be recommended to student and physician alike.

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MODERN TREATMENT YEARBOOK 1955—A Yearbook of Diagnosis and Treatment for the General Practitioner. Edited by Sir Cecil Wakeley, Bt., K.B.E., C.B., LL.D., M.Ch., D.Sc., F.R.C.S., F.R.S.E., F.R.S.A., F.A.C.S., F.R.A.C.S., Fellow of King's College, London; Senior Surgeon, King's College Hospital. Published for the Medical Press by Bailliere, Tindall & Cox, Ltd., Distributed in U.S.A. by Williams and Wilkins Company, Baltimore, 1955. 344 pages, $6.00.

This 337 page book is composed of 36 monographs on modern treatment by British authors. It is the 21st volume in the yearbook series edited by Sir Cecil Wakeley.

In general, it is well done and can be recommended to the American reader who would like to explore a little beyond the "beaten path."